FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING (AIDAC)

Thursday, January 22, 2015

8:00 a.m. to 2:18 p.m.

FDA White Oak Campus

FDA White Oak Conference Campus

Building 31, The Great Room

Silver Spring, Maryland

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C O N T E N T S

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. MOORE: All right. Good morning. I want to welcome everybody to the Anti-Infective Drugs Advisory Committee meeting today. I'd like to first remind everybody to please silence your cell phones, smartphones, and any other devices if you've not already done so. I'd also like to identify the FDA press contact, Stephanie Yao. There you are. Hi, Steph.

My name is Tom Moore. I'm the acting chairperson for today's meeting. I'll now call this meeting of the Anti-Infective Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves. Let's start down on the right. Dr. Robinson?

DR. ROBINSON: Patrick Robinson with Boehringer Ingelheim. I'm the industry representative.

DR. WATERMAN: Paige Waterman from the

Department of Defense.

DR. NEELY: Michael Neely. I'm associate professor of Pediatrics and Infectious Diseases at University of Southern California and Children's Hospital, Los Angeles.

DR. MOORE: Dr. Bennett, I believe you're joining us by phone. Go ahead, Dr. Bennett.

DR. BENNETT: Oh, I'm sorry. This is John Bennett, NIAID.

DR. MOORE: Thank you. Sorry. Thanks for joining us. I'm sorry didn't give you advance warning. You'll be following Dr. Neely when I go around the table, but I'll give you a heads up.

DR. BENNETT: Thank you.

DR. MOORE: Go ahead.

DR. CHILLER: Tom Chiller, the deputy chief of the Mycotic Diseases Branch at the CDC in Atlanta.

MR. BYRD: Good morning. Christopher Byrd, patient representative from Winter Park, Florida.

DR. ANDREWS: Ellen Andrews, consumer representative from the Connecticut Health Policy

Project.

DR. CAPPELLETTY: Diane Cappelletty, Pharm D, associate professor, College of Pharmacy and Pharmaceutical Sciences, and department chair, Pharmacy Practice.

DR. MOORE: Dr. Tom Moore, University of Kansas in Wichita.

DR. SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. SCHEETZ: Mark Scheetz, Midwestern University and Northwestern Medicine.

DR. SHYR: Yu Shyr, professor of biostatistics, Vanderbilt University.

DR. FOLLMANN: Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. DIXON: Cheryl Dixon, statistical reviewer, FDA.

DR. WEINSTEIN: Ed Weinstein, medical officer, Division of Anti-Infective Products, FDA.

DR. ALEXANDER: John Alexander, medical team Leader, Division of Anti-Infectives.

DR. NAMBIAR: Sumati Nambiar, division director, Division of Anti-Infective Products, CDER, FDA.

DR. COX: Good morning. Ed Cox, director, Office of Anti-Microbial Products, CDER, FDA.

DR. MOORE: Thank you. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that the members of the media

are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it on to Lieutenant Commander Jennifer Shepherd.

Conflict of Interest Statement

DR. SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the Anti-Infective Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under l8 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts,

grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today, the committee will discuss New Drug Applications 207500 and 207501 for isavuconazonium sulphate capsules and isavuconazonium sulphate for injection sponsored by Astellas Pharma Global Development Incorporated, respectively, for the proposed indications of treatment of invasive aspergillosis and mucormycosis. This is a particular matters meeting during which specific matters related to Astellas NDAs will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that

Dr. Patrick Robinson is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Robinson's role at this meeting is to represent industry in general and not any particular company. Dr. Robinson is employed by Boehringer-Ingelheim Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. MOORE: Thank you, Jennifer.

We will now proceed with the FDA presentation. We'll go with Dr. Alexander's

introductory remarks.

FDA Introductory Remarks - John Alexander

DR. ALEXANDER: Good morning. My name is John Alexander. I'm a team leader in the Division of Anti-Infectives, and I'd like to welcome everybody to this morning's NDA discussion of isavuconazonium. Isavuconazonium has a trade name of Cresemba. Isavuconazonium is a prodrug of isavuconazole, a triazole antifungal agent. The NDA applicant is Astellas Pharma U.S., Incorporated.

The discussion today is about two NDAs: one for capsules with each capsule providing the equivalent of 100 milligrams of isavuconazole and a separate NDA for vials for injection. So each vial has enough powder, which when reconstituted would provide the equivalent of 200 milligrams of isavuconazole.

The proposed indications for both of the NDAs are the same. They are invasive aspergillosis and invasive mucormycosis. Astellas has received orphan drug designation for isavuconazonium for

both of the proposed indications.

Orphan drug designation is mainly based on the rarity of the condition in the United States. Invasive fungal infections, in general, are considered fairly rare, but I would note that even among the different types of invasive fungal infection, there's rare like Aspergillus and then there's really rare like mucormycosis, and that does play a role in the types of studies that have conducted for this submission.

So today's discussion will focus on the clinical trials demonstrating the efficacy and safety of the product. The first study is CL0104 of invasive fungal disease caused by Aspergillus species or other filamentous fungi. This was a randomized, double-blind study. It involved a comparator, voriconaole, and a noninferiority design, and this was the main source of data to support the aspergillosis claim.

The second clinical trial, CL0103, was a study of patients with renal impairment or patients with invasive fungal disease caused by rare molds,

yeasts, or dimorphic fungi. This was an open-label, prospective study, involved no concurrent comparator. So we're talking about a historical control when looking at the mucormycosis claim, and this was the main source of data to support the mucormycosis claim.

So as an outline for the day, after my presentation, there'll be presentations made by the applicant on the NDA applications, followed by FDA presentations.

Dr. Cheryl Dixon, the statistical reviewer will be reviewing the results of the aspergillosis study, and Dr. Edward Weinstein will be reviewing the results of the mucormycosis trial and the overall safety of the product. After lunch, there'll be an open public hearing, and then the questions to the committee and committee discussion.

So as a prelude to the end of the day, it's always good to go over the questions at the beginning. The first question is a voting question. Has the applicant demonstrated

substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of invasive aspergillosis? If yes, provide any recommendations concerning labeling. If no, what additional studies, analyses are needed?

The second question is also a voting question. Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of mucormycosis? If yes, provide any recommendations concerning labeling. If no, what additional studies or analyses are needed? Thank you.

DR. MOORE: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all

participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they have with the firm at issue such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with the sponsor's presentations.

Applicant Presentation - Bernhardt Zeiher

DR. ZEIHER: Good morning. My name is Bernie Zeiher, executive vice president of global development at Astellas. I'd like to thank you for the opportunity to present the data supporting isavuconazole for the treatment of both invasive aspergillosis and invasive mucormycosis.

The agenda for our presentation will include my initial discussion regarding the compound overview and clinical pharmacology. Dr. Andrew Ullmann, from the University of Würzburg and chairman of the Data Review Committee for the phase 3 aspergillosis study, will discuss the disease background and unmet medical need. Ms. Maher and Dr. Mujais will then present then efficacy and safety data supporting both indications. I will then return for concluding remarks regarding the overall benefit/risk assessment.

In addition to Dr. Ullmann, we have a number of outside experts available to take your questions. All experts have been compensated for their time and travel to today's meeting.

The chemical structure of isavuconazonium is shown here. It is a novel prodrug. After IV or oral administration, it is rapidly hydrolyzed to the active moiety, isavuconazole, shown in red. Isavuconazonium itself is not detected in the blood after completion of the IV infusion or oral

administration. Only the active moiety, isavuconazole, and the inactive cleavage product, which is rapidly cleared, are detected.

While isavuconazole is poorly soluble, the prodrug isavuconazonium is highly water-soluble and there's no need for cyclodextrin in the IV formulation. Thus, isavuconazonium overcomes solubility and bioavailability issues that have been associated with other mold-active azoles.

Moving forward in this presentation, we will refer to the product as isavuconazole, or ISA even, for simplicity.

Now, let me describe the mechanism of action. This figure depicts the fungal cell wall and cell membrane. Ergosterol is a key component of all fungal cell membranes and serves many of the same functions as cholesterol in animal cell membranes.

The cytochrome P450 enzyme, lanosterol 14alpha-demethylase, is the enzyme which converts lanosterol to ergosterol. ISA like other triazole antifungals inhibits this enzyme and thereby

depletes ergosterol in the fungal cell membrane, which compromises its structure and function.

Furthermore, there's an accumulation of methylated sterol precursors, which inhibits fungal cell growth. This mechanism of action translates into ISA having a broad spectrum of antifungal activity, including yeasts, molds, and dimorphic fungi.

Here you see the in vitro activity profile of ISA and that of amphotericin and voriconazole, or vori, against a number of mold pathogens. The ISA spectrum of activity is very similar to that of vori, with the exception that it also has activity against Mucorales, which is a mold pathogen that can mimic invasive aspergillosis.

In vivo, this in vitro profile translates into reductions in fungal tissue burden and increases in survival in animal models of invasive aspergillosis and pulmonary mucormycosis. Like other azoles, the pharmacokinetic and pharmacodynamic parameter of AUC/MIC correlates best with outcome.

Given this spectrum of activity, the clinical development program sought to demonstrate efficacy and safety in both invasive aspergillosis and mucormycosis.

Clinical development was initiated by our partner, Basilea, in 2002. Forty phase 1 studies were conducted to fully characterize the pharmacokinetics and drug-drug interaction potential of ISA. The phase 3 program was initiated in 2007. In 2010, Astellas licensed the development rights and assumed sponsorship for the phase 3 clinical studies.

Interactions with the Division of Anti-Infective Products and former division of Special Pathogens and Transplant Products were held at regular intervals throughout the development program. Importantly, agreement was reached on the primary endpoint of our phase 3 aspergillosis study of all-cause mortality through day 42 in the ITT population and the 10 percent noninferiority margin.

In 2013 and 2014, the FDA granted Qualified

Infectious Disease Product, or QIDP status, and orphan drug status for both invasive aspergillosis and mucormycosis. The NDA was submitted in July 2014 and included data from 44 clinical studies, which enrolled more than 2100 subjects, nearly 1700 of whom received at least one dose of isavuconazole.

Taken together, the preclinical and clinical data support the proposed indications for isavuconazole as treatment of adults with invasive aspergillosis and invasive mucormycosis.

Now, let me describe the clinical pharmacology of isavuconazole. The clinical pharmacology has been well-characterized in 40 studies designed to evaluate bioavailability, food effect, pharmacodynamics including a Thorough QT study, pharmacokinetics in special populations, and drug-drug interaction potential.

These studies demonstrate dose proportional increases and exposure with either IV or oral dosing. The oral dose is rapidly absorbed with 98 percent bioavailability. There's no evidence of

a gastric pH or food effect, and taken together, these attributes allow for milligram for milligram dose switching between IV and oral formulations.

ISA has a large volume of distribution of approximately 450 liters. It's metabolized predominantly by CYP3A4 with less than 1 percent of unchanged drug excreted by the kidneys. It has a long elimination half-life of approximately 130 hours, which enables once daily administration. And there's no need for dose adjustment in the elderly, mild to moderate hepatic impairment, or in patients with mild, moderate, or severe renal impairment including end-stage renal disease.

Because ISA, like other azoles, inhibits a fungal cytochrome P450 enzyme, there is potential for inhibition of human CYP enzymes. Therefore, extensive drug-drug interaction studies were performed to characterize this risk.

ISA is a mild to moderate inhibitor of CYP3A4 and is associated with a twofold increase in exposures of sensitive substrates of CYP3A4 such as midazolam or sirolimus. This contrasts with

voriconazole, which results in a 10- to 11-fold increase in exposure of midazolam and sirolimus, and helps to explain why sirolimus is contraindicated in the voriconazole label.

ISA does not inhibit CYP2C9 or 2C19, whereas vori increases prothrombin time twofold and omeprazole concentrations fourfold. ISA induces CYP2B6, whereas vori is a mild inhibitor of 2B6.

In summary, ISA has a more clinically manageable drug-drug interaction profile as compared to that of voriconazole.

Now, I'd like to discuss the rationale for the dose regimen, which was used in phase 3. This figure depicts mean simulated trough concentrations of 200 milligrams once daily administered to healthy volunteers. Given its long elimination half-life, it's approximately a fourfold accumulation and steady state is reached in about 3 weeks.

Importantly, trough concentrations may not be above the MIC90 for aspergillosis species for up to a week. In critically ill patients with

invasive fungal disease, this is obviously too long to reach therapeutic exposures, and thus we utilized a loading dose regimen in phase 3 and in our proposed label.

The blue curve represents the mean simulated trough concentration using the phase 3 loading dose regimen, which consists of 200 milligrams administered every 8 hours for the first 2 days, followed by 200 milligrams once daily. Using this regimen, trough concentrations above the MIC90 for Aspergillus are achieved within 24 to 48 hours and then maintained throughout the treatment period.

As we will present, this dose regimen was demonstrated to be well-tolerated and effective in the treatment of both invasive aspergillosis and mucormycosis.

So having completed my overview, I'd like to turn the presentation over to Dr. Ullmann, who will present the disease background and unmet need for both indications. Dr. Ullmann?

Applicant Presentation - Andrew Ullmann

DR. ULLMANN: Thank you, Dr. Zeiher.

I'm Andrew Ullmann, and as the chair of the ESCMID Fungal Infection Group and head of the Infectious Disease Division, Würzburg, my main clinical focus is the care of patients with immune suppression, including invasive fungal disease. I would like to turn your attention to the background of these infections and our unmet medical need.

There are several key points to remember about invasive fungal infections. First, they typically occur in patients with severely compromised immune systems, such as patients with hematologic malignancies, particularly those with severe and prolonged neutropenia.

Second, these infections are considered very rare. Approximately 12,000 U.S. patients per year are diagnosed with invasive aspergillosis. Invasive mucormycosis is even more rare, with only about 500 patients per year diagnosed. However, these are likely to be underestimated due to the difficulty in diagnosis. Even when properly diagnosed and treated, there is a high morbidity and mortality associated with these infections.

Finally, there are limited therapeutic options, particularly for patients who fail treatment or are intolerant to the current available therapies.

Let me first discuss invasive aspergillosis and describe a typical patient with such an infection. A typical patient might be a person treated for acute myeloid leukemia who presents with non-specific clinical symptoms such as fever and cough with or without sputum production. The differential diagnosis in such a patient is vast and requires urgent medical evaluation, including appropriate chest radiographic imaging.

Here you see a CT finding of nodular infiltrates that would suggest invasive fungal disease. In this case, we would immediately start the patient on a mold-active antifungal treatment while additional diagnostic testing is performed. Given the challenges in diagnosis, the ERTC and MSG have established standard diagnostic criteria, providing a legal of certainty for use in clinical trials.

Patients who have predefined host factors and radiographic signs are considered to have possible disease. To classify patients as either proven or probable, we used mycologic criteria such as cultures, histology, or galactomannan testing. However, even with aggressive attempts to obtain samples, many patients failed to have their diagnosis confirmed.

Therefore, we initiated mold-active antifungal treatment not only in patients with proven or probable disease, but also in those with possible disease, unless an alternative etiology is identified. It is essential to treat patients even with possible disease.

As shown in the data reported by Chamilos and colleagues, they reported autopsy data for more than 1000 patients with hematologic malignancies treated at MD Anderson Cancer Center and found that 31 percent of patients had invasive fungal disease at autopsy. Importantly, 75 percent of these infections were not diagnosed prior to death. Even in the era of galactomannan testing, diagnosis

remains difficult.

In 2008, Sinko and colleagues reported on a consecutive series of 38 allogeneic hematopoietic stem cell transplant recipients who died. All had extensive autopsies performed. Ten patients died with fungal disease. Despite the regular use galactomannan testing, a diagnosis of proven or probable invasive fungal disease prior to death could only be established in 4 of 10 autopsy-verified cases.

In the remaining 6 patients, invasive mycosis was revealed only by post-mortem histology. Three of these patients did, in fact, have invasive aspergillosis. Two patients were diagnosed with pulmonary mucormycosis and one with disseminated candidiasis.

The key point is that patients continue to die of invasive fungal disease that may not be diagnosed prior to death, despite diagnostic criteria and algorithms for the use of antifungal therapies. Thus, we need to have a high index of suspicion and even treat those with possible,

meaning suspected, disease.

For the last 12 years, the standard of care is voriconazole, as published in guidelines by the IDSA and societies in Europe. In 2002, Herbrecht and colleagues reported on a large, randomized, active control study of voriconazole versus amphotericin B deoxycholate in invasive aspergillosis.

As depicted in this figure, overall survival was significantly improved with voriconazole treatment versus amphotericin B treatment followed by other licensed antifungal agents. Voriconazole is a triazole antifungal with excellent in vitro activity against Aspergillus species. However, it has several limitations. It has no activity against Mucorales, which may clinically mimic Aspergillus.

Intravenous and oral formulations are available. However, cyclodextrin is required as a solubilizing agent in the IV formulation, and this limits use in patients with moderate to severe renal impairment.

Voriconazole also has some pharmacokinetic characteristics that complicate its use. These include non-linear pharmacokinetics related to its actual metabolism. In addition, CYP2C19 significantly contributes to its metabolism, and this enzyme has considerable genetic variability.

The label also advises administration of voriconazole on an empty stomach due to the food effect. Additionally, the previous described drug-drug interactions complicate use in critical ill patients on multiple medications.

Voriconazole also has been associated with hepatic toxicity, dermatological reactions, including photosensitivity, and in some cases cutaneous malignancies. QT prolongation also has been associated with voriconazole use.

Additionally, a unique safety risk of voriconazole includes visual disturbances. These disturbances have been described as enhanced perception of light, blurred vision, changes in color perception, and photophobia.

In voriconazole clinical trials, elevated

liver function tests, rash, and visual disturbances were the most often treatment-related adverse events that led to discontinuation of treatment. Together, these pharmacologic and safety characteristics make voriconazole a challenging drug to use. Even if considered the drug of choice for invasive aspergillosis, the side effects may require discontinuation of therapy. Thus, it is imperative to have more treatment options for our patients.

Now, let me turn to the current standard of care for the treatment of invasive mucormycosis. Though diagnostic criteria are similar to those of aspergillosis, to date there is no serologic biomarker for mucormycosis. Thus, the diagnosis relies on invasive procedures of the affected area. So when it involves an organ such as the lung, it can be much more difficult to confirm the diagnosis.

It's particularly challenging to confirm diagnosis in patients after chemotherapy, since biopsies are frequently contraindicated because of

severe pancytopenia.

Here you see a CT scan of a patient with a cavitary and nodular lesion in the lung, which was confirmed by histology and culture to be due to mucormycosis. However, this scan could have been easily interpreted as invasive aspergillosis.

When it involves the upper airway or skin, it's easier to obtain tissue samples. In many of these patients, the infection can cause extensive necrosis, necessitating extensive surgical debridement. If recognized and treated early in the clinical course, treatment may reduce the amount of surgical resection and disfigurement.

Systemic antifungal treatment usually requires long-term therapy, but without appropriate treatment, the disease is basically fatal. Unfortunately, the approved armamentarium of antifungals is very limited, and frequently, we need to move into a salvage situation, which in most cases ends in death. Clearly, active agents are needed to treat this disease.

Amphotericin B is standard of care for

treatment of invasive mucormycosis since it harbors a broad in vitro activity against many fungi including mucormycosis. It is available in an IV formulation only. This formulation is associated with infusion reactions and especially severe renal toxicity, which is associated with prolonged stay in the hospital and mortality.

Amphotericin B deoxycholate is the only FDA approved therapy for mucormycosis, but it has an unacceptable toxicity profile. Lipid formulations were developed to reduce the toxicity associated with amphotericin B deoxycholate, and they are recommended in the first-line treatment for mucormycosis by the European Society of Clinical Microbiology and Infectious Diseases.

Given the rarity of this infection, treatment guidelines have been based upon clinical case series and expert opinion. The largest review of mucormycosis was reported by Roden and colleagues in 2005. In her review of all reports of mucormycosis in the English language literature, only 929 eligible cases from 1940 to 2003 were

identified.

An analysis of mortality based on treatment revealed a 97 percent mortality rate with no treatment, 39 percent mortality with amphotericin B deoxycholate, and 31 percent mortality with lipid formulations of amphotericin B.

Favorable trends with lipid formulations, along with the improved safety profile, support use of lipid formulations as first-line therapy. In addition, Chamilos and colleagues underscore the importance for early initiation of appropriate treatment.

Mortality rate at 12 weeks increased from 49 to 83 percent when Mucorales active antifungal therapy was delayed 6 or more days after symptom onset. These data clearly demonstrate the need to start antifungal therapy against Mucorales early on in the process of disease.

In summary, diagnostic procedures and the mortality associated with this disease remains challenging. Diagnostic procedures are unsatisfactory since CT scanning does not reliably

differentiate between the two diseases. We have no reliable biomarkers, which could rule out these fungal diseases, and culture or cytology is frequently false negative.

So far, we only have two drugs available for the primary treatment of filamentous fungi. We need additional therapeutic options, since the morbidity and mortality remain high. Voriconazole is the recommended first-line treatment in aspergillosis, but has significant pharmacokinetic and safety limitations. Additionally, it has no activity against Mucorales.

For patients with mucormycosis, the only approved antifungal agent is amphotericin B deoxycholate, which was introduced in the 1950s and has significant toxicity profile. Given the diagnostic challenges and limited therapeutic options, it would be particularly important to our patients to have agents with activity against both infections due to the similarity of clinical presentations.

Now, I would like to turn the presentation

over to Ms. Maher who will discuss the efficacy data supporting isavuconazole.

Applicant Presentation – Rochelle Maher

MS. MAHER: Thank you, Dr. Ullmann. I am Rochelle Maher, and I am the global project lead for the isavuconazole development program. I have the opportunity this morning to show you the efficacy outcomes from the two phase 3 studies that support this NDA application.

I will first discuss study 0104, which provides the primary support for the invasive aspergillosis indication. I will then discuss study 0103, which provides the primary support for the invasive mucormycosis indication.

The first study, 0104, was open to enrollment for patients with invasive fungal disease caused by Aspergillus species or other filamentous fungi. Patients with proven, probable, or possible disease, as assessed by the investigator, were eligible for enrollment, which required evidence of host factors indicating high risk for disease and radiologic findings consistent

with invasive fungal disease. Patients were categorized as proven or probable if they also met protocol criteria for mycology.

This was an international, double-blind, randomized, controlled study comparing isavuconazole to standard dose voriconazole with a treatment duration up to 84 days. The pre-randomization stratification variables were hematopoietic stem cell transplant, active malignancy, and geographic region.

This was a noninferiority study design. The primary endpoint was all-cause mortality through day 42. The prespecified noninferiority margin was 10 percent. The assumed all-cause mortality rate was 20 percent, which was based on the voriconazole registration study for invasive aspergillosis that was referenced by Dr. Ullmann.

With 80 percent power and a one-sided 2.5 percent significance level, this yields a sample size of 510 patients. A key secondary endpoint was the success rate, which was defined as complete or partial response at the end of

treatment. The overall response is based on clinical, radiologic, and mycologic factors.

Response outcomes were determined by an independent, blinded data review committee, which I will refer to as the DRC. The DRC charter was based on criteria set forth by the EORTC/MSG professional organizations in Europe and the U.S.

I will now show patient disposition and baseline characteristics for study 0104. 516 patients received at least one dose of study drug and comprised the ITT population. Both the isavuconazole and voriconazole treatment groups had 258 patients.

This population was the prespecified data set used in analyzing the primary endpoint of all-cause mortality through day 42. The modified ITT or mITT population included patients who were determined to have proven or probable invasive fungal disease as determined by the DRC.

There were 143 patients in the isavuconazole treatment group, and 129 patients in the voriconazole treatment group. The mycologic ITT or

myITT population consisted of mITT patients specifically with invasive aspergillosis based on cytology, histology, culture, or galactomannan criteria. Additional analytical populations were also analyzed and are included in your briefing book.

For those patients who had a pathogen identified, the most common was Aspergillus fumigatus, followed by flavus. Half the mITT population included patients with probable disease for which mycological evidence was based only on serum galactomannan. The protocol specified serum galactomannan criteria, included either 2 serum values greater than or equal to 0.5 or 1 value greater than or equal to 0.7.

Patient demographics were well-balanced between the treatment groups. The mean age was 51 years in both treatment groups. Both groups had slightly more males than females and were predominantly white.

The underlying conditions of patients are representative of those at the greatest risk for

aspergillosis. Most patients had hematologic malignancies; a majority had an active malignancy or were neutropenic. Greater than 40 percent were receiving T-cell immunosuppressants, and approximately 15 to 20 percent underwent hematopoietic stem cell transplant or used corticosteroids. Active malignancy in hematopoietic stem cell transplant were prespecified, randomization stratification variables.

In addition, there was a third stratification variable, geographic region. Approximately 11 percent, 40 percent, and 48 percent of patients coming from North America, Western Europe, plus Australia and New Zealand and other regions, respectively.

The countries contributing the highest enrollment in the other category are Israel, Thailand, India, China, and Russia. The distribution was balanced between the treatment groups for the stratification variables.

The mean treatment duration of study drug

administration was close to 47 days for both treatment groups. Intravenous therapy was administered for a mean of 8 to 9 days. All patients started on IV therapy, and approximately 80 percent switched from IV to oral during the course of the study.

Let's now look at the efficacy results from the 0104 randomized, double-blind study. The primary objective of the study was met. The all-cause mortality rate at day 42 in the ITT population for the isavuconazole treatment group was 18.6 percent and 20.2 percent for the voriconazole treatment group.

For the primary analysis, the adjusted treatment difference was calculated using the stratification variables. In the upper bound of the 95 percent confidence interval, 5.7, is less than the prespecified 10 percent noninferiority margin.

It is important to note that the survival status was known for all but 5 patients: 3 isavuconazole patients, and 2 voriconazole

patients. These 5 patients were considered to have died for the primary analysis. It is also important to note that the mortality rate in the voriconazole treatment group was as expected and the same as that used for the study design assumptions.

Here is a forest plot of the primary endpoint of all-cause mortality through day 42 in the ITT population. The blue circle represents the adjusted treatment difference with the associated 95 percent confidence interval. The dotted line reflects the 10 percent noninferiority margin.

Day 42 all-cause mortality in the mITT and myITT populations were also analyzed and shown here with the upper bound of the 95 percent confidence intervals well below 10 percent. Day 84 all-cause mortality is shown for these three analysis populations.

The FDA also defined an alternative mITT population, which used a different galactomannan criteria than the protocol specified criteria, based on recent FDA draft guidelines. The FDA

specified galactomannan criteria included either two serum values greater than or equal to 0.5, or a single serum or BAL value greater than or equal to 1. Overall, there was nearly 90 percent concordance between the protocol and FDA mITT populations.

On the next slide, we have included the day 42 and day 84 outcomes for the FDA mITT population to the forest plot. You can see that collectively these data demonstrate consistent efficacies across analysis populations and across time points.

These figures represent Kaplan-Meier survival curves for the ITT and mITT populations. The blue line represents the isavuconazole treatment group, and the pink line represents the voriconazole group, providing additional support that the survival probability is similar between the treatment groups over time.

Presented here is another forest plot of all-cause mortality through day 42 by baseline characteristics of clinical interest. Outcomes in these subgroups support similar efficacy in

patients who have key risk factors for poor outcomes. Additional subgroups are also provided in your briefing book.

This slide represents the independent blinded DRC's assessment of overall response. As you recall, this was considered a key secondary endpoint. Success included complete and partial responders. As displayed, the success rates were similar between the treatment groups. While not shown here, outcomes for the FDA mITT population are essentially the same.

In summary, the totality of data from this large, randomized, controlled clinical trial demonstrate that isavuconazole is effective for the primary treatment of invasive aspergillosis. The primary efficacy objective was met, demonstrating that isavuconazole is non-inferior to voriconazole, based on the primary endpoint of all-cause mortality through day 42 in the ITT population.

All-cause mortality outcomes were consistent across analysis populations, subgroups, and across time points, demonstrating the robustness of the

results. In addition, the DRC assessed key secondary endpoint success rate supports the conclusion from the primary analysis.

The second study, 0103, was open to enrollment for patients with rare fungal diseases. This study was an international, open label, single-arm study of isavuconazole. Eligible patients were adults with a wide range of rare molds, including Mucorales, yeasts, and dimorphic fungi.

The isavuconazole dosing regimen in the 0103 study was the same as in the 0104 study, except patients could start on oral therapy and continue for up to 180 days. Eligible patients required either primary therapy or were refractory to or intolerant of other antifungal therapy.

One hundred forty-six patients received isavuconazole in this study. Of these, 46 patients enrolled with invasive mucormycosis; 38 had an invasive mold infection caused by a single Mucorales order pathogen. This excludes 8 patients with mixed fungal infections that included a

Mucorales order pathogen.

Of these, 37 were determined to have proven or probable disease by the DRC and are included in the mITT population, which is the focus of the data presented here today. These patients were categorized as either primary, refractory, or intolerant as confirmed by the DRC.

It should be noted that this study represents one of the largest series of prospectively evaluated and systematically treated patients with invasive mucormycosis.

Baseline characteristics are shown here. A majority of patients had an underlying hematologic malignancy, predominantly active. Several patients were on T-cell immunosuppressants or had a stem cell or solid organ transplant. The population is reflective of those who would be candidates to receive isavuconazole in the clinical setting.

The mean duration of study drug administration was 133 days with half the patients being treated between 84 and 882 days. Intravenous therapy was administered for a median of 10 days.

Let's now turn to the efficacy results from study 0103, which against support the invasive mucormycosis indication. The success rate for the DRC assessed overall response at the end of treatment was approximately 31 percent, with half of those assessed as complete response and half, a partial response.

Given the rapidly fatal nature of mucormycosis, a clinically relevant response could be defined as success together with stable disease. This reflects approximately in 60 percent of the patients in this study. The all-cause mortality rate through day 42 was 37.8 percent, and through day 84 was 43.2 percent.

Since this was a single-arm study, we used several external data sources to put our results into context. An indication for invasive mucormycosis must be viewed in the context of the totality of evidence.

The Agency has specified that for rare fungal pathogens, such as Mucorales, efficacy be demonstrated in a minimum of 20 well-documented

cases. Those data could be evaluated in the context of a larger randomized controlled trial, such as our 0104 study in invasive aspergillosis, along with appropriate animal models and a literature evaluation, including mortality rates in untreated and treated literature controls. In addition to that, Astellas conducted a matched case control analysis.

I have already discussed the large randomized control trial in invasively aspergillosis, so I will now turn to the animal models.

The efficacy of isavuconazole was assessed in experimental models of mucormycosis. Shown here are outcomes of the primary intratracheal model in neutropenic mice, which was developed and validated via NIH funding, specific to test drugs against mucormycosis.

In this model, mice infected with Rhizopus oryzae initiated antifungal therapy 8 hours post-infection at doses that approximate expected human exposure. The efficacy of isavuconazole,

which is represented in blue, is superior to that of placebo controls, which is represented in red. Also, ISA outcomes were similar to that of liposomal amphotericin B, which is represented in green.

A significant decrease in fungal burden has also been demonstrated, in the lung, the target organ, and in the brain, the secondary target organ. ISA outcomes were similar to that of liposomal amphotericin B.

So let's now turn to the literature evaluation that was conducted. As Dr. Ullmann presented, a review article by Roden includes invasively mucormycosis cases reported from 1940 to 2003. A second, more recent paper by Skiada also reported mortality rates in amphotericin-treated and untreated patients from 2005 to 2007.

The blue dots represent the mortality rate along with the 95 percent confidence interval for amphotericin-treated patients and patients who did not receive treatment.

We also obtained data from the Fungiscope

database, which is a multicenter, international, active and contemporary observational study established in 2003. It is a large collection of information on rare fungal infections and includes data on over 150 cases of invasive mucormycosis, including outcomes in amphotericin-treated and untreated patients. Using these three data sources, a meta-analysis was conducted and is shown here.

These data represent a clear amphotericin treatment effect in this nearly universally fatal disease. The 0103 isavuconazole data I presented previously is added here for comparison. These data show a clear isavuconazole treatment effect similar to that of amphotericin.

In addition to the animal models and the literature evaluation, we conducted a matched case control analysis to provide a more contemporary comparison more carefully controlling for key risk factors. We collaborated with Dr. Cornely, who is here with us today, to develop the methodology for case managing and analysis.

Patients from study 0103 who were treated with isavuconazole as primary therapy; the group with the least confounding factors were matched to controls treated with amphotericin preparations for primary therapy from the Fungiscope database.

The case matching used three primary criteria considered relevant factors predictive of outcome. The first was severe disease, which was defined as patients with CNS involvement or disseminated disease. The second was whether or not they have an underlying hematologic malignancy. And the third was surgical resection or debridement intended as therapeutic intervention for invasive mucormycosis.

The matching activity was conducted, independent of the sponsor, by a physician blinded to outcomes on both treatment groups. Each of the 0103 cases could be matched to up to three controls. Day 42 mortality rates were then analyzed.

All 21 of the study 0103 cases treated with isavuconazole for primary therapy were matched, and

a total of 33 controls were identified. This slide shows the disposition of patients by the three matching criteria. Study 0103 cases had a somewhat higher proportion of patients with severe disease.

I will now show the mortality rates. The mortality rates for study 0103 cases treated with isavuconazole was 33 percent. The mortality rate for the Fungiscope controls treated with amphotericin was 39 percent. The mortality outcomes are shown here with 95 percent confidence intervals.

Again, these data represent contemporary patients matched for key risk factors, treated for primary therapy, the least confounded patient group, and demonstrated similar mortality rates.

You have seen the rest of these data previously, now in the context of the matched cases and controls. Taken collectively, you can see that mortality outcomes in patients treated with isavuconazole are better than those who did not receive treatment. Also, outcomes are similar to that of amphotericin-treated patients, which is

consistent with our animal models.

In summary, the totality of data support an invasive mucormycosis indication. In animal models, isavuconazole demonstrated superior outcomes relative to placebo and similar outcomes relative to liposomal amphotericin.

Clinically, isavuconazole showed better efficacy relative to untreated controls and similar efficacy relative to amphotericin B from the literature and matched controls.

To recap, the efficacy of isavuconazole has been demonstrated for the treatment of invasive aspergillosis as well as for invasive mucormycosis. In the large randomized controlled trial in invasive aspergillosis, the primary study objective was met. Isavuconazole was non-inferior to voriconazole for all-cause mortality, and outcomes were consistent across populations, subgroups, and time points. In invasive mucormycosis, the preclinical and clinical data support the efficacy of isavuconazole.

I will now invite Dr. Mujais to address the

safety findings from the isavuconazole development program.

Applicant Presentation - Salim Mujais

DR. MUJAIS: Thank you, Ms. Maher. Good morning. I'm Dr. Salim Mujais from the Medical Science Group at Astellas. In summarizing pertinent safety information from our development program, I will begin by describing to you the overall safety population and extent of drug exposure.

I will then focus on study 0104, which provides context for safety evaluation against current recommended therapy. We will explore standard safety measures such as death, SAEs, most common SAEs, and most common AEs.

I will also elaborate on a few categories of adverse events of interest. I then will describe to you findings pertinent to cardiac repolarization and consistency of safety across subgroups and studies.

The safety profile of isavuconazole has been well-characterized with the large global safety

population. In total, over 1600 subjects have received isavuconazole in our clinical development program. In phase 1 studies, over 1100 subjects were exposed to isavuconazole in standard PK studies, pharmacodynamic studies, examining effects on cardiac repolarization, and an extensive drug-drug interaction program.

The phase 2 program involved two studies. The first examined the use of isavuconazole in the treatment of esophageal candidiasis, and the second, the use of isavuconazole in fungal prophylaxis in neutropenic patients with acute myeloid leukemia.

Finally, the phase 3 program for the proposed indications included 403 subjects who received isavuconazole in two separate studies already described to you by my colleague.

The extent of patient exposure in the two phase 3 studies is illustrated on the slide. A substantial number of subjects have received isavuconazole for durations relevant to the proposed indications, with a median exposure of

45 days for aspergillosis and 94 days in study 0103 for mucormycosis and rare molds.

The proportion of subjects receiving isavuconazole for more than 4 months consists mostly of subjects with mucormycosis or rare molds. Longer therapy duration was allowed in these patients by protocol and was prescribed as deemed necessary by their managing physicians.

For what follows in this presentation, I will focus on information from the controlled randomized study 0104, including discussion from other studies as needed. Study 0104 allows us to assess safety in a rigorous design where reporting of safety events is done under blinded conditions.

Further, the use of the active comparator voriconazole permits the study findings to be put into context of current recommended therapy. Additionally, the study size allows exploration of safety in subgroups of interest.

Allow me first to remind you briefly of a few pertinent baseline characteristics of the population of study 0104 relevant to our discussion

of safety.

The population of the study has an inherent high morbidity and is characterized by high prevalence of hematologic malignancy with most patients immunocompromised because of neutropenia, chemotherapy, use of T-cell immunosuppressants, and use of steroids. This morbidity characteristics were balanced between the two treatment groups.

The table shows a high level summary of safety findings from study 0104. Adverse events leading to death were similar in both groups. Half the subjects experienced serious adverse events. Adverse events were very common and reported in almost all patients across treatment groups, an expected finding considering the clinical characteristics of this patient population.

Despite the high incidence of overall adverse events, differences were noted between the two groups in drug-related adverse events. Finally, adverse events leading to permanent discontinuation of study drug were lower in isavuconazole versus voriconazole.

This slide presents the general categories of adverse events leading to death by system organ class exceeding 1 percent in either group and listed by descending frequency for isavuconazole. The majority of reported adverse events leading to death were in the system organ categories of infection, the pulmonary complications of infection, and the underlying malignancy.

The most frequently reported serious adverse events occurring in at least 5 percent in either group are shown on this slide, again by system organ class. The serious condition of the patients requiring treatment with antifungals is underscored by the frequency of serious adverse events and the categories in which they occurred. Again, they reflect the underlying disease, and the infection, and its complications. Overall, serious adverse events were similar in both treatment groups.

The 10 most common adverse events regardless of causality assessment are shown on this slide. GI-related adverse events predominated in both groups.

Looking now at the overall adverse events by system organ class, we observe broad concordance between the two groups in the majority of system organ class categories, except for three categories known to represent events of interest for voriconazole and mentioned by Dr. Ullmann; namely, skin, eye, and hepatobiliary disorders. I will presently discuss these categories in greater detail.

The rate of events in the skin and subcutaneous tissue disorder was lower for isavuconazole than for voriconazole. The difference was accounted for mostly by the frequencies of adverse events of rash, erythema, and drug eruption.

The rate of events in the eye disorder category was lower for isavuconazole than for voriconazole. The difference is due mainly to the frequencies of visual impairment and photophobia. The rate of events in the hepatobiliary disorder category was also lower for isavuconazole than for voriconazole.

Because of the importance of effects on the liver for the azole class, we expanded the exploration of hepatic safety by a structured analysis of lab parameters obtained during the study. Elevations in liver enzymes were observed during the study in both treatment groups. Maximal liver enzyme measurements, at any time post-baseline, were classified by their degree of excursion from the upper limit of normal.

There was a trend for liver enzyme abnormalities during the study to be more frequent in the voriconazole group, particularly for the more severe categories of transaminases.

We also looked at concurrent abnormalities of liver enzymes and bilirubin, which are used to identify patients with potentially more severe disease. We used the nominal lab definition of Hy's law of concurrent elevations of transaminases exceeding 3 times the upper limit of normal, bilirubin exceeding 2 times the upper limit or normal, and alkaline phosphatase less than 2 times the upper limit of normal.

There were 3 patients fulfilling the nominal lab definitions of Hy's law in the isavuconazole group and 7 patients in the voriconazole group. A detailed review of the records of patients in both treatment groups revealed potential alternative etiologies for the observed laboratory abnormalities such as concomitant sepsis, multi-organ failure, and/or concomitant use of hepatotoxic drugs.

Next, I'd like to describe changes in cardiac repolarization as manifested in alterations in the QT interval on ECGs. ECG QT interval prolongation is a recognized class effect of azole antifungals. A Thorough QT study was undertaken in healthy volunteers to determine whether such a class effect exists for our compound.

As is standard for such studies, we utilized the recommended isavuconazole therapeutic dose with loading doses followed by 200 milligram per day maintenance, and the supratherapeutic dose with the same loading doses followed by 600 milligram per day maintenance.

In contrast to other azoles, isavuconazole caused dose-dependent QTc shortening. The shortening averaged 13 milliseconds at the Cmax of the proposed therapeutic maintenance dose of 200 milligrams per day. The mechanism of this shortening was studied and may be related to an inhibition by isavuconazole of a calcium channel, in contrast to the other azoles, which inhibit predominantly potassium channels. A more detailed comparison of the two mechanisms and effects is described in the Astellas briefing book.

A pronounced shortening of the QT interval is observed in the congenital short QT syndrome, in extremely rare channelopathy that is associated with serious ventricular arrhythmias. However, the clinical relevance of drug-induced QTc shortening has not been established.

We first examined whether the observed QTc shortening in the Thorough QT study reduced the QT segment length to below thresholds of clinical interest. The slide shows QTc thresholds of clinical interest, 480 and 500 milliseconds for QT

prolongation and 330 and 300 milliseconds for QT shortening. No normal volunteer on either the therapeutic dose or supratherapeutic dose crossed the thresholds of interest.

Next, we examined the frequency of QTc changes in study 0104. QT interval measurements were determined from centrally read ECGs in a blinded fashion. It is important to remember that ECGs during the clinical study are obtained under conditions different from those of the Thorough QT study, which is very carefully controlled.

Lengthening and shortening of QTc were observed in both groups. This likely speaks to the complexity of clinical factors and concomitant medications affecting the QTc in the patient population. Fewer isavuconazole-treated patients than voriconazole-treated patients had QTcF values exceeding 480 milliseconds. A small number of patients had QTcF lower than 330 milliseconds in both groups. Very few patients in either treatment group had extreme values of QTcF exceeding 500 milliseconds or less than 300 milliseconds.

Having determined the rarity of extreme excursions in the QTc interval, we next explored potential clinical correlates of changes in cardiac repolarization. We needed to look at adverse events that could potentially be linked to changes in cardiac repolarization, either shortening or prolongation.

In clinical studies when encountering an agent that has an effect on the QT segment, we tend to use a standard search for adverse events. This is commonly referred to as the Torsade de Pointes standardized MedDRA query, as indicated on the slide, considering that Torsade de Pointes is the arrhythmia commonly associated with QT prolongation.

Because there is no parallel standardized search for arrhythmias associated with QT shortening, we applied the standardized search used for QT prolongation. This is a conservative search approach that captures events potentially associated with ventricular arrhythmias. This is why non-specific terms such as syncope, loss of

consciousness, and non-specified cardiac arrest are included.

The incidence of this constellation of adverse events in isavuconazole-treated patients was 5.8 percent, compared to 7.3 percent in voriconazole-treated patients. There is an apparent difference between the treatment groups for syncope and loss of consciousness, with 7 events of syncope and 3 events of loss of consciousness in the isavuconazole group. A detailed review of these patients revealed no reported arrhythmias and no QT shortening or prolongation on ECGs.

To conclude our QT discussion, a shortening of cardiac repolarization interval was observed in healthy subjects in the Thorough QT studies. This was not replicated in the clinical studies, where we observed both QT shortening and QT prolongation in both groups. There did not appear to be a clinical correlate to the electrocardiographic finding as assessed by an analysis of adverse events potentially associated with changes in

cardiac repolarization.

To complete the safety analysis, we looked at whether the observed differences in adverse events between isavuconazole and voriconazole in the system organ classes for eye, skin, and hepatobiliary disorders persisted in select subgroup analysis.

The subgroups examined are shown on this slide. Details of the analysis have been provided in your briefing book. In summary, the difference between the two treatment groups in the incidence of adverse events for skin, eye, and hepatobiliary disorders was preserved in the majority of subgroups examined.

Safety findings from other studies in the clinical program were concordant with the findings of the 0104 study. In particular, the safety profile of patients with invasive mucormycosis was consistent with that observed in the 0104 study, taking into account the more common rhino-cerebral involvement in patients with mucormycosis.

To illustrate the consistent safety profile

across the two phase 3 studies, I will briefly present the overall safety findings for patients receiving isavuconazole in both studies.

The overall safety profile was similar in the two studies. Despite the longer duration of drug exposure in study 0103, with a median 94 days versus 45 days in study 0104, the frequencies of study drug-related AEs and AEs leading to permanent discontinuation of study drug were similar in the two studies, suggesting that the safety profile was stable with longer exposure.

The following two slides describe our approach to risk management for the safety risks determined from the clinical development program, azole class-specific risks on this slide and isavuconazole specific risks on the following slides.

While isavuconazole is a new molecular entity, the azole class is well precedented. The risks similar to the azole class are classified as either identified or potential and will be represented appropriately in the label.

Hepatotoxicity and infusion-related reactions are two known azole class effects. Infusion-related reactions were rare in our clinical program, however, they are still classified as an identified risk.

Other potential risks observed with the azole class, which have either not been observed in our program to date or were confounded by other factors, include severe cutaneous reactions, embryo-fetal toxicity, and drug exposure in breastfed infants.

Azole class labeling is also proposed for the USPI. In addition, standard postmarketing fungal surveillance will be conducted to look for evidence of emerging drug resistance. Standard pharmacovigilance processes to collect and analyze safety information will be implemented.

Relative to the other azoles, the only unique potential safety risk was exposure-related QT shortening. The clinical significance of this electrographic finding is uncertain, given that no clinical correlate has been identified in the

clinical program.

To manage this potential risk, proposed labeling will describe the effects of isavuconazole on the QT segment and will include a contraindication for familial short QT syndrome. This labeling language is similar to that of rufinamide in anti-epileptic with known QT shortening.

In summary, isavuconazole has a well-characterized safety profile. This safety profile is favorable, particularly compared to voriconazole, in the areas of skin disorders, eye disorders, and hepatobiliary disorders. Isavuconazole shortens QTc, while voriconazole results in lengthening of QTc. The safety profile of isavuconazole is generally similar across the two target indications.

Now, I will return the lectern to Dr. Zeiher for concluding remarks.

Applicant Presentation - Bernhardt Zeiher

DR. ZEIHER: Thank you, Dr. Mujais. As you've heard, invasive aspergillosis and invasive

mucormycosis are life-threatening infections occurring predominantly in immunocompromised patients. Their rarity and unmet medical need are exemplified by the orphan and QIDP status for both indications.

For invasive aspergillosis, voriconazole is the recommended first-line treatment, but has a number of limitations including its pharmacokinetic and safety profile. For mucormycosis, the only antifungal agent approved by the FDA is amphotericin B deoxycholate, which is only available IV and associated with significant toxicity.

Isavuconazole has the potential to provide a needed alternative for both indications. In terms of its clinical pharmacologic profile, isavuconazole has predictable pharmacokinetics, moderate PK variability with dose-proportional increases in exposure, high oral bioavailability with bioequivalence and AUC, an absence of a gastric pH or food effect.

Together, these attributes allow for

interchangeable IV and oral dosing. It also has a long half-life, enabling once daily dosing, no cyclodextrin in the IV formulation, and a more manageable drug-drug interaction profile.

For the indication of invasive aspergillosis, study 0104 demonstrated that isavuconazole has non-inferior efficacy compared to voriconazole on the primary endpoint of all-cause mortality through day 42.

The DRC assessed secondary endpoint of overall response also supported non-inferior efficacy. These efficacy outcomes were robust and consistent across analysis populations, medically important subgroups, and time points.

For the indication of invasive mucormycosis, study 0103 demonstrated similar mortality outcomes to what has been reported in the literature and the case matching study with amphotericin B. Furthermore, the outcomes are consistent with our preclinical models and are significantly better than no treatment, which has been reported to have a near 100 percent mortality. While uncontrolled,

these data support isavuconazole's clinical effectiveness in mucormycosis.

Turning to the safety profile, the adverse event profile was overall similar to that of other compounds in the azole class. The main exception is exposure-related QT interval shortening. Although a clinical correlated has not been identified, proposed labeling will address this risk.

Relative to voriconazole, isavuconazole demonstrated a favorable safety profile with a lower incidence of study drug related adverse events and a lower incidence of hepatobiliary, eye, and skin reactions, which have been associated with voriconazole use. In addition, isavuconazole may be used in the renally impaired patients and has no signal nephrotoxic effects.

In conclusion, isavuconazole has a favorable benefit/risk profile. It has predictable pharmacokinetics, non-inferior efficacy compared to the gold standard of care in aspergillosis, clinical effectiveness in mucormycosis, and a

favorable safety profile.

So it addresses a number of the limitations of the available treatment options and provides a needed alternative for both indications. Thank you for your attention, and we will now take your questions.

Clarifying Questions

DR. MOORE: We'll proceed to clarifying questions. I'll start off, Dr. Zeiher. In the briefing materials, it was mentioned that the pharmacokinetics were slightly different in Asians. And I was wondering if the sponsor would like to offer -- or the sponsor had a hypothesis to explain that.

Secondly, in the overall analysis of the data, did that subgroup demonstrate any specific differences in mortality or morbidity.

DR. ZEIHER: So first, I'll let Dr. Keirns address the clearance differences in Asians.

DR. KEIRNS: Dr. Keirns from the clinical pharmacology group at Astellas. We conducted a dedicated study in Chinese subjects, following the

same dosing approach as some other clinical pharmacology studies in Western subjects. And I have a comparison here of the pharmacokinetics.

The mean AUC value in the Chinese subjects was approximately 50 percent higher than in the Western subjects. And we checked to what extent this was accounted for by body weight, which was responsible for a small part of that difference, but not for the majority of it.

So the majority of the difference of higher exposure in Asians is due to a factor that we've not yet identified.

DR. ZEIHER: Now, getting to your question also about outcomes in these patients, so in our briefing book, table 18, there is a forest plot, which includes white and non-white individuals. And if anything, the point estimate in non-white individuals favored voriconazole. Most of the non-white individuals were Asian subjects.

When we look at this population, there were different numbers of patients in the two groups. And as we've examined it more carefully, we didn't

clearly identify any reason specifically for why there was some imbalance. We think it may be more related to just numbers of patients. I think importantly, they didn't have lower exposure, which would have led to less efficacy.

DR. MOORE: Thank you.

Dr. Bennett, you're joining us by phone. You had a question.

[Dr. Bennett's comments/questions stated on the record were inaudible. The following questions were submitted in writing.]

DR. BENNETT: I would like to know if patients in the original Basilea trial were included on the final data. If so, was the blind broken for the "futility analysis" Basilea did in the two year pause?

I also want to know if the proven and probable aspergillosis patients are in the MyITT group, whereas the mITT group also has possible cases?

Please explain why the study endpoint was changed when Astellas began the trial.

DR. ZEIHER: Thank you. So let me first address the reason for changing the endpoints. So as Dr. Bennett mentioned, there was a pause in the enrollment, which ended up being approximately two years at which -- and Astellas took over development rights in 2010 and became the sponsor of the phase 3 study.

We did, as outlined in the briefing book, change the primary endpoint. And the reason for this really had to do with the need to justify the noninferiority margin. The noninferiority margin, which was originally specified in the original protocol, was a 20 percent noninferiority margin around a DRC assessment overall response.

Trying to justify this, we did not think was really feasible. And so in terms of trying to comply with recent guidances with the FDA around formal justifications of a noninferiority margin, you need to have information on what's the placebo outcomes or untreated outcomes, as well as outcomes in your comparator and so forth.

So what we did was we embarked upon doing a

formal justification and determined that we needed to do it with all-cause mortality at day 42. Furthermore, all-cause mortality at day 42 has been reported to be predominantly, in this disease, associated with a fungal infection, rather than underlying malignancies.

The other aspect is it's unambiguous. When you look at in terms of missing information, things like radiography, it's much better. And as we described in our data presentation, only 5 patients did we not know the mortality outcomes at day 42. So those were the primary drivers to change it.

The second question, which actually I think was your first question, were all patients included in the analysis? Yes. So all patients were included in the analysis; both patients from the initial portion of the study over 300 patients had been enrolled, and then the additional patients that were enrolled after Astellas took over were included in the final analysis.

Furthermore, the DRC assessment of fungal disease, their disease assessment, as well as their

assessment of response, was done at the latter part, after we had taken over, so that all patients were assessed using the same sorts of criteria in terms of -- and in a similar time frame of their assessment.

The last question really related to the futility analysis. So there was a futility analysis done before Astellas assumed sponsorship. This was done by an independent data monitoring committee. We were unaware of the -- it was not unblinded to the sponsor. There was no -- and this was not a basis for the decision for us to change the endpoint. It really was based upon the need to justify the noninferiority margin and the fact that we thought it was very relevant and unambiguous in terms of the interpretation of the data.

DR. BENNETT: Thank you. That's very clear.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: I have several questions. The first question is can you turn to slide 40, the baseline conditions? Yes. I would like to know what kind of randomization method you guys applied.

DR. ZEIHER: So this was done via central IVRS --

DR. SHYR: Which method used to stratify -- you minimization, randomization. Which method did you really use?

DR. ZEIHER: They were stratified into the -- it was a stratified randomization based on -- into blocks. So there were 12 potential strata.

DR. SHYR: Because I do know, you look at your table here, you still have some 5 percent difference imbalance. Do you know the reason? If you really did stratify using block randomization, you should control within certain numbers.

DR. ZEIHER: So the ones -- you know, I don't have an exact explanation. I do know that sometimes investigators had a little bit of trouble with the definition of active malignancy. So this was what we called uncontrolled malignancy. And in fact, what the definition of that was really that they did not have evidence that they had been in remission. So that may have accounted for some of

the imbalance, but I don't have any other explanation for why there was some differences there.

DR. SHYR: Okay. Second question. You already answered. Your subgroup analysis, you only show part of that on slide 49. But in your briefing book, figure 18, on page 78, you already mentioned that, in the non-white group performs much worse, not much worse, a little bit. Yes. So this table, you can see non-white is a little bit worse. You already mentioned also that for other regions -- I assumed the other region was all Chinese.

DR. ZEIHER: Yes.

DR. SHYR: Okay. So you already say you couldn't identify the reasons.

DR. ZEIHER: No, we looked at this. And in fact, actually the way -- actually patients even from India and other Asian continent also classified themselves as Asian, but it may be worth looking at some of our country distribution. So what I'll display here, these are the top 10

enrolling countries, and also the region is listed with them. So you can see Israel was the largest country in the other region.

But what you do see is a fair bit of variability as you look down the various regions. So some of the ones that would have Asian patients, include regions like Thailand, India, China, as you mentioned. And you see a fair bit of variability as you get into these smaller groups.

As we tried to look at this further, we didn't identify any, what I'd say culprit, in terms of major imbalances in the group. And whether combination is a factor, such as if they had hematologic malignancy and something else, we don't know. We could not -- we did look carefully and did not identify any sort of major difference.

DR. SHYR: Perhaps you should have spent more, because even point estimate is close to that 10 percent, the non-inferior, that margin.

My next question, you did mention you have 5 patients you didn't know the survival status. Those are missing. And you assume all those

5 patients were dead. Did you do the sensitivity analysis to assume those 5 patients, they have different status?

DR. ZEIHER: Yes. So maybe I'll first put up briefing book table number 13. We had two preplanned sensitivity analyses. One was a minimum risk method and you can see those results and the corresponding confidence intervals. The upper bound of the confidence interval there was 5.6. And then without adjustment for stratification factors, that was 5.6.

The other things we also did was look just at -- we also did assess mortality even doing a worst case analysis. And what I'll show here is a worst case analysis.

So that would be basically assuming the isavuconazole patients died, and all the voriconazole people where you don't know their outcome, they survived. And you can still see that the adjusted difference at day 42 was 0.3 with an upper bound of 6-4. And again you can see that day 84 was 0.7 and upper bound of 8-3.

DR. SHYR: Correct. Last question, can you move to slide 63? Okay. Here, I'm very curious to know, you say you are matching here and you used the matching criteria. And you say up to three controls for each 0103 cases. Do you know how many of them have a multiple match among those 21?

DR. ZEIHER: Yeah.

DR SHYR: So all 21 at least have one match.

DR. ZEIHER: Correct.

DR. SHYR: Some of them have multiple, right?

DR. ZEIHER: Correct.

DR. SHYR: And then my question is did you do propensity score matching method instead of using three -- can you do the propensity score matching? Do you have all the covariates available?

DR. ZEIHER: Yes, so we -- well, first to answer about the propensity score, we did not do that. But let me first answer your question about how many matches we had for each case. And if I can put up table 32 from your briefing book, you

can see that 5 patients -- 5 cases had 3 controls, 2 had 2, and 14 had just 1 match.

If I also could pull up from the presentation, I believe it's the slide 64 from the core deck. So if we could display that. You can see the main area where there was not as good a matching had to do with severe disease. And we could identify -- we were not able to identify as many matches for patients who had CNS involvement and disseminated disease.

So that's why you see that there were less controls that matched that. And in fact what it means is that, if anything, the cases from 0103 had more severe -- had a higher proportion, had severe disease than our controls, and would be expected to have a somewhat higher mortality even.

DR. SHYR: And last question, have you ever tried any sophisticated statistical modeling to do this match control, like generalized estimating equation method, instead of generating two confidence intervals separately?

DR. ZEIHER: So we did do an analysis where

we took the controls and we identified what factors in the controls were predictive of outcome in the controls, and then applied that to our patient population, our cases. And if anything, what it did was it predicted that our case group would have an even higher mortality than what we've seen. So in fact -- let me just actually put up this slide.

It was a complicated method, as you sort of alluded to, in the sense that what's depicted here on the bottom portion of the slide -- I'll just focus you there -- in terms of the all-cause mortality was 33 percent, and the observed and the Fungiscope was 39 percent.

So when you predict -- obviously is you use that population to predict a mortality, the bottom row, the very bottom row, would be 39 percent. Of course, if you use that, you would get the same mortality. If we use that information to predict what we would have seen in our cases, it would have been 47.

So it again reconfirms what we saw here, suggesting that the matches probably were a little

less severe than what we had in our cases.

DR. SHRY: Okay. Thank you.

DR. MOORE: Dr. Cappelletty?

DR. CAPPELLETTY: I have two questions for you guys. In the IV preparation with the precipitation issue, is there a time dependent process such that if the IV bag is mixed and then sits for a few hours, does the amount of precipitation increase? Is there a limitation with preparation and administration?

DR. ZEIHER: Let me first bring up the slide from the core presentation with the structure, just to remind you. The precipitate that's actually in the IV is actually -- it's treated as an impurity, but in fast it's actually isavuconazole, the active moiety, because isavuconazole, a small amount, it's impossible to completely get rid of isavuconazole in the IV drug product, and it's very insoluble. So that's really what that precipitate is.

In terms of is there a time dependency of developing it, there will be instructions not to shake the bag. That's one of the things you don't

want the pharmacist who's preparing the IV solution to do because that can actually increase the amount of hydrolysis. And the other thing is that it should be refrigerated if it's not going to be infused right away because there could be more hydrolysis if it's not kept refrigerated.

DR. CAPPELLETTY: And then my second question is, is there a dose-dependent effect on the adverse effects related to liver, skin, or any of the ocular related activities?

DR. ZEIHER: So we did not -- basically, the phase 3 program investigated one dose regimen really. So it was just the 200 milligram dose, first with the loading dose of 600 within the first 2 days, and then 200 milligrams per day. So there really is not an ability to look at some of those adverse events for any dose dependency.

Although in our Thorough QT study, we did study 600 milligrams. It was a relatively short duration. And the main things we began to see in that group were things, like some people complained of hot flushes, nausea, some anxiety, and dry

mouth. You did see that. And we actually had patients who needed to discontinue from that. Even though they were healthy volunteers, they had to discontinue just because of some of those other side effects.

DR. CAPPELLETTY: In that Asian subpopulation that had higher PK profile, did they experience a higher amount of adverse effects compared to others?

DR. ZEIHER: Let me try and answer it specifically related to some of these adverse effects that we looked at. We did look and see if in our phase 3 program, for example, if there was any exposure related adverse effects. And we didn't actually see that there was not a relationship between exposure there in phase 3. And overall, the population seemed to be very similar across -- in the safety profile, seemed very similar, as Dr. Mujais presented.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: Like the others, I had more than one question. I have three. Could you just

clarify for me, the 98 percent bioavailability of the oral preparation, was that in healthy volunteers only, or do you have bioavailability data in sick patients?

DR. ZEIHER: So the information that I provided was in healthy volunteers. So we did do healthy volunteer study, IV, oral, well-controlled circumstance. We also did studies with omeprazole to see with a gastric pH and also looked at food effect. So although we don't have a formal bioavailability study in patients, those data would suggest that it's not different.

Furthermore, I would say the exposures are, if anything, somewhat higher in the patient population, including when we look at IV and oral. The reason likely is that in our sick population, some of the clearance may be somewhat reduced. But we don't have a formal bioavailability study.

DR. NEELY: I ask because voriconazole is notorious for that. The bioavailability is much lower in patients than it is -- and it didn't really come out pre-approval.

My second question is -- sorry, I'm not a statistician, so a little bit naivete, could you just let me know, the controls, the matching controls, were they all unique, independent individuals or did you recycle?

DR. ZEIHER: No, they were all unique.

DR. NEELY: Okay. Thank you. And my final question is, I looked at the article that was referenced for the short QT syndrome, and it just says it's a rare disorder. Perhaps it's not really known how many people suffer from this.

Are you planning to put in the package insert that you would recommend a baseline screening ECG before starting therapy?

DR. ZEIHER: We did not have that in our proposal, but we'd be happy to discuss that with the FDA if that's recommended.

DR. NEELY: Thank you.

DR. MOORE: Thank you. Dr. Robinson?

DR. ROBINSON: Yes, a couple of questions. First, on the efficacy side, there's a substantial subpopulation that did not meet the mITT criteria?

DR. ZEIHER: Correct.

DR. ROBINSON: And I noticed doing some simple subtraction that actually their mortality rates were relatively similar, were actually pretty similar to mITT population. Can you describe the non-mITT population a little bit more, and is there any hypothesis as to what these patients may have represented in terms of undiagnosed or underdiagnosed fungal disease?

DR. ZEIHER: Yeah. So just a couple things. So as was described in terms of the job of our DRC was really to classify patients as either proven, probable, or possible, or no IFD. Overall, out of the population, the DRC assessed 48 subjects as not having sufficient evidence to say they had invasive fungal disease. The remainder of patients were assessed as either proven, probable, or possible. So the biggest bulk of those are the possibles. And in general, the reason they're possibles and not proven or probable is because of the mycologic criteria.

Many of these patients have -- well, to meet

the criteria to have possible disease, they had to have host factors such as neutropenia, and they had to have radiographic findings, but they didn't meet the mycologic criteria, usually serum galactomannan or they had a biopsy that didn't grow anything. So that's what they are.

Importantly, these patients still have a high mortality, as you noted. And in fact, as also Dr. Ullmann pointed out in his presentation, many of these people have invasive fungal disease. It may just be that they have an insufficient fungal burden so that you can detect it, or you can't get sufficient samples, so the false negative rate is high.

Thus, in our trial, what we did was we treated all of them because that would be standard of practice. Unless you had an alternative diagnosis, you would treat these individuals.

DR. ROBINSON: Thank you. The other question relates to the cutaneous reactions. Among the severe cutaneous reactions, were there any patients that had Stevens Johnson or toxic

epidermal necrolysis or DRESS syndrome?

DR. ZEIHER: Maybe I'll let Dr. Mujais speak to what we saw with respect to cutaneous reactions.

DR. MUJAIS: Let me first directly answer your specific questions. We have not yet observed any cases of Stevens Johnson syndrome in the clinical program. The cases that we have observed are shown on the slide. And you can see we have 1 case of an exfoliative dermatitis and 2 cases of erythema multiforme in the isavuconazole group. And the cases shown in voriconazole group are described on this slide.

DR. ROBINSON: And were any of the exfoliative cases severe enough to be potentially life-threatening?

DR. MUJAIS: None of the cases were life-threatening, and they did not result in study drug discontinuation.

DR. MOORE: Thank you. Mr. Byrd.

MR. BYRD: Thank you. This question might actually be more proper for FDA staff, but I'm curious to know from the applicant, whether any

patients under the age of 18 have been tracked or studied, and if not, what the reasons are for not tracking those patients.

DR. ZEIHER: The trials were intended largely to enroll adults. I believe we did have one patient who was just under 18 when it was enrolled and had special consent obtained. But basically, all of the trials were designed to study adults. And this has to do really with trying to demonstrate efficacy, safety in an adult population before you would investigate in pediatrics. We do recognize that it would be important to investigate in the future.

MR. BYRD: Thank you.

DR. MOORE: Dr. Scheetz?

DR. SCHEETZ: I have a couple questions. My first question relates to the pharmacokinetic, pharmacodynamic metric, and you suggested in the presentation that AUC is predictive of outcome. I assume that comes from the animal data. My question also comes from your supplied material on page 91 on study 0104. It did not appear that MIC

predicated outcome.

So I'm wondering what you think about the relevance of your animal data for your PK/PD endpoints moving forward, is there any link to being able to predict human outcomes?

DR. ZEIHER: Let me make a couple of general comments, and then I'll ask one of my colleagues to help speak more. So I would say, first of all, you're right, that in our non-clinical species, we would say that AUC/MIC was the best predictor for outcomes in terms of fungal burden, outcomes. And so we did look for and do PK/PD analyses to look for evidence within our trial that there was, in fact, some relationship.

Part of why we may not have seen any relationship within the trial may have to do with either the numbers of patients that you have at different MICs, or the fact that we think actually we're probably above the critical threshold. For ethical reasons, you don't study multiple doses. You want to make sure you're above the target.

So it may be, given the exposures that were

achieved -- because of the exposures that were achieved, we're not dropping below any critical threshold. And our patients are above that threshold, so that they would see response, and that would be our thoughts. But maybe I'll ask Dr. Andes if he wants to comment any further on predictivity of these findings with other agents.

DR. ANDES: David Andes, professor and chief of infectious disease at University of Wisconsin, expertise in PK/PD. We would not have expected, based on the animal model studies, to see a threshold in the clinical trials when one looks at the AUC that patients had in the trial and the MIC distribution observed for the MICs in the clinical isolates.

The animal model studies I think provide proof of principle for the clinical program in that the exposures in animals were similar to the exposures in patients, and the MIC distribution that was studied in the animal models is similar to the MIC distribution that was observed in the clinical trials, and we saw success against those

isolates in the animal models.

DR. SCHEETZ: My second question moves forward from Dr. Shyr's point. Also in 0104, there was a difference at baseline in the patients with regard to their neutropenia status. As a clinician, that would be my -- the main thing that I would be concerned that could potentially pollute the data. Did you run any analyses that controlled for neutropenia to see if that had an impact on your overall outcomes?

DR. ZEIHER: So first, if we can show the -- from the core slide, I think it would be 49. So again, if you look at presence of neutropenia, again the outcomes -- if we look at that row, very similar outcomes in isavuconazole and voriconazole. So when you look at that subgroup who had or did not have neutropenia, I would say the outcomes are very similar.

We did also do an exploratory analysis looking at resolution of neutropenia because that actually has predictive value in terms of outcomes. Those who tend to remain neutropenic do much worse.

I'll show this slide, which -- what's shown here first are all-cause mortality at day 42 in the mITT population versus the ITT population in patients who either continued neutropenic or resolved their neutropenia. And you can see similar outcomes in both treatment groups, whether it be the mITT or the ITT population, and whether their neutropenia resolved or remained.

DR. SCHEETZ: And then just one last final question. Is there any concern that you could have particulate matter basically forming back the primary drug after the inline filter and if that line is not flushed, the patient then receive perhaps more particulate matter than had been presented before the inline filter?

DR. ZEIHER: Yes. I mean, we don't believe so. I think the -- there are a couple things to point out. As I was mentioning, I think this is the active moiety. The main reason for the filter relates to exceeding USP limits although it's actually a very small amount.

We've done analyses to look at patients who

did not get the filter, and we did not see any safety findings, because there were a small number of individuals in the phase 3 study who they neglected to use a filter at the site, and we did do a careful safety analyses of those patients and did not identify an issue there.

DR. MOORE: All right, thank you.

Dr. Bennett, you have another question? Sorry, there's a delay here in the room until we get the phone hookup. Are we ready?

DR. BENNETT: Can you hear me now, Tom?

DR. MOORE: Sorry. Okay. Yes, Dr. Bennett. Go ahead.

DR. BENNETT: I have a question as to what the final number of patients of proven and probable was in [indiscernible] isavuconazole of 04, and I believe the number is 104, because if you don't have mycological proof, you can't be proven or probable.

I'm a little perplexed by the mITT as labeled proven or probable in one of the slides, because if you don't have mycological proof, you're

not proven or probable. So my question being, is the final number 104 or not?

And the second question has to do with the 03 study and the group of 21 patients who had primary therapy and they're the ones that were important and used for the comparison. Six of those patients of the 21 completed the therapy and lived; 6 patients died and were not able to complete the therapy; but 9 are listed as other outcomes.

That suggested to me that in this trial that patient s were -- that someone decided maybe they needed amphotericin B or other drugs were added. I'm a little curious. They're very tiny groups, but I'd like to know more about those 9 patients. That's the end of my question. Thank you.

DR. ZEIHER: Okay. So I'm not sure I understood the first question. Did -- was anyone able to repeat --

DR. MOORE: Dr. Bennett, I'm sorry. The connection is not ideal, so I apologize. Would you be able to restate that question? And we're going

to -- can we hear Dr. Bennett now? Sorry, we're going to -- how about now?

DR. BENNETT: Can I try again?

DR. MOORE: Yes, sir. We can hear you now.

DR. BENNETT: How many proven and probable cases of aspergillosis were in the isavuconazole arm? Was it 104 or a larger number?

DR. ZEIHER: How many were proven or probable? Let me get the -- so if we can have the briefing book table on the distribution of patients with proven, probable, possible disease.

DR. MOORE: And let me just -- and sorry, Dr. Bennett, I apologize for this. I'm being told if you would -- if you're going to ask a question, if you could pick up the phone and -- I guess their communication would be better that way, rather than through speaker phone. I'm sorry about that.

Sponsor, you understood the question?

DR. ZEIHER: Yes. This will have the numbers and hopefully address this question. Let me put this up. This actually has the outcomes, but also has the Ns for the different patients, so

I think the only question was, what were the numbers that were classified as proven or probable?

So you can see for proven, probable, it's 29 proven, 114 probable. There's also 88 possible, and then 27 were classified -- within the isavuconazole group, we had no IFD. And you can see then the associated mortality rates, which when you look across are very similar between treatment groups.

So hopefully that addresses the outcome in those patients. I think the other question was what happened to 9 other patients from study 0103. So maybe if we can first -- so maybe we'll first go up CO58, and I think you're referring to -- just to clarify, Dr. Bennett, are you referring to patients who did not have complete or partial response? Or are you referring to patients who did not have complete, partial, or stable disease?

DR. BENNETT: No, I'm asking about 9 who didn't complete treatment and who didn't die. Why didn't they complete treatment? Because it's very difficult to know what the drug does if you don't

die or you don't complete treatment. So what occurred that led to the drug being stopped?

DR. ZEIHER: So I think what we'll do is maybe after the break, we can get some more detailed information on each specific case. But in general, patients were discontinued either because it was viewed that they may be progressing or some of them actually discontinued because they were about to die. Part of that could be some of the reason, but why don't we get you some more information about those specific 9.

I do know that 7 of the patients who discontinued actually discontinued after day 84. So sometimes they were actually well beyond even the initial 12 week period.

DR. BENNETT: Okay. Thank you.

DR. MOORE: Okay, Dr. Follmann?

DR. FOLLMANN: I have a couple questions. I think it would be easiest if you first went to slide CO54. This concerns study 103, the one arm study for muco. So if we look the slide, earlier you mentioned that there were 146 patients who were

given ISA, and we focus here on the 37. We looked at their death rate which was about 38 percent. Then you also looked at the primary proven or probable group, which had a death rate of around 33 percent. But you don't report the death rate in 75 percent of these people who got your drug, and because you need to use empiric therapy before you can get a definite diagnosis, this would be the way it's administered in the field.

So I'm curious about the death rate for the 75 percent who aren't reported here. If we would approve this drug, we'd want some evidence that that death rate is similar to those who would get alternate therapy amphotericin.

So do you have any analyses concerning those patients death rate?

DR. ZEIHER: Sure. So first let me clarify the trial. So study 0103 included patients who had a variety of fungal infections, not just mucormycosis. So in fact there were patients enrolled who had invasive aspergillosis who were not eligible for 0104 because they had renal

impairment.

According to the label, IV voriconazole because it has cyclodextrin shouldn't be administered to patients who have moderate to severe renal impairment. So there's a subgroup of patients who had invasive aspergillosis. And then there were a variety of other fungal infections.

All of these were independently adjudicated in terms of what their infection was by a DRC, to what they were. And what I'll put up is a table from your briefing book, which is table 78, I believe it's in one of your appendices, which talks about some other of these infections.

So in some instances, if we even just start on the far right, they had mixed infection. Many of these actually had Mucorales as part of that mixed infection. So there's 15. You can see mortality rates. There's non-candida yeast, dymorphic fungi which are most of your endemic fungi, other mold species, and then filamentous fungi.

The reason the Mucor was selected out was

because, A, we had a significant number of these that we could well-characterize and had discussions and also saw the high unmet medical need, particularly in this population and the overlap with our aspergillosis population.

DR. FOLLMANN: Right. So what I'd be interested in, if you had a similar slide for people who were treated with amphotericin. And also, the death rates for people who you couldn't categorize. Because 75 percent of the people will get this drug, and we'd like to know that their death rate would be similar to those who got amphotericin. So like another comparison with controls that you didn't do is what I would be interested in.

DR. ZEIHER: I guess the -- in patients who had Mucorales infection? Because I think again, the outcomes --

DR. FOLLMANN: No, not in Mucorales. You gave 146 patients this drug, and you report in the death rate in those with proven and probable. And you compare that to people who got amphotericin.

So 75 percent of the people you show a part of the death rate there, I'd like to see that, and all 75 percent and I'd also like to see the death rate in those who got amphotericin. Like another case-controlled analysis.

This is what you would do, like in an intent-to-treat analysis, you want to compare everyone who got the drug, even if they didn't have the indication or not, to those who got the comparator, just to ensure that overall, it's not harming people in aggregate for the vast majority, or the majority who don't have the infection that you're interested in.

So anyway, that's my point. I hope it's clear enough.

DR. ZEIHER: Let me first comment. If you look at that list of various fungal infections, not all of them would amphotericin be the standard of care --

DR. FOLLMAN: Right.

DR. ZEIHER: -- which is sort of the problem in trying to do that comparison. And some of the

numbers in those is very -- outcomes, for example, in dymorphic fungi, are tremendously different than some of the other fungal infections that we're talking about like fusarium, scedosporium. So trying to actually make that comparison isn't necessarily the right way.

I guess our point is we're trying to -- the proposed indications really would be for aspergillosis and mucormycosis. At this stage, we would not be proposing that this is appropriate treatment for, let's say, dimorphic fungi and so forth.

DR. FOLLMAN: Right, but you're giving it to them empirically because you couldn't identify them at baseline. And so they'll be getting the drug and be like -- or I'd like some assurance that they're not harmed by this medication.

DR. ZEIHER: So would it be helpful -- what I can't do is give you comparison for amphotericin, because it wouldn't be fair, because some patients might be refractory or amphotericin might be the appropriate treatment. We could give you what was

the pooled mortality from the overall study, which is the whole 146.

DR. FOLLMAN: No, I was thinking more like in a Fungiscope. You did a case control study for patients who didn't get your drug. They got control therapy, mostly amphotericin, I assume. And something like that I think would be the kind of analysis that I think would be interesting.

DR. ZEIHER: Yes. I don't have that, at least outside of a mucormycosis population.

DR. ZOLLMAN: Fine. Right. Then I have a couple other questions. You did a matched analysis. There were 37 with proven or probable mucormycosis, and you did a matched analysis on the 21 that were primary, and you didn't match on the other ones. Could you explain the reasoning behind that?

DR. ZEIHER: So the main reason is because -- well, it really relates to the ability to identify comparable sorts of patients. Because, basically, if you look at our population that were either refractory or intolerant, they've already

received -- in general, would have received amphotericin.

So you would have compared patients who have either failed amphotericin or they've -- they've been on amphotericin for three months, but now they're getting renal insufficiency and need something to treat, versus patients who are getting primary therapy. So it was really the least confounded and the cleanest population to try to make the comparison.

DR. FOLLMAN: Okay, thanks. Then I have one final question. You displayed some of the matching criteria, but I was wondering if you matched on whether they had -- the people in the Fungiscope data set had proven or probable mucormycosis. Because the 21 you did have proven or probable, it seems like that would be a natural thing to match on, but you didn't mention that.

DR. ZEIHER: So the inclusion criteria required that -- actually, maybe I'll let Dr. Cornely speak to it, to the process that was taken. But they had to have proven or probable

mucormycosis for them to identify match. But would it be helpful for him to describe the process?

DR. FOLLMAN: No. So in the Fungiscope database, they had proven or probable?

DR. ZEIHER: Yes.

DR. FOLLMAN: Okay, that's what I wanted to know.

DR. ZEIHER: Yes.

DR. FOLLMAN: So good.

DR. MOORE: If there are no other questions to the sponsor, we will go ahead and take a break. We will reconvene at 10:30. Panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves or with any member of the audience. Thank you.

(Whereupon, a recess was taken.)

DR. MOORE: Okay, we'll go ahead and start the next session. We'll now proceed with the FDA presentations, if we're ready.

FDA Presentation - Cheryl Dixon

DR. DIXON: Good morning. I am Cheryl Dixon, the statistical reviewer for the

isavuconazonium NDA submissions. I will be presenting the division's assessment of the clinical efficacy of the isavuconazonium for the treatment of invasive aspergillosis. As you will see from my presentation, we are in general agreement with that which was presented by the applicant earlier this morning.

In my presentation, I will be discussing the phase 3 trial 0104 that was conducted to provide the primary support for the invasive aspergillosis indication. I will provide a brief overview of the design of the trial and discuss the justification of the noninferiority margin used to assess the trial.

I will then go over patient disposition and demographics, followed by the efficacy results for the primary endpoint and the key secondary endpoint, and end with some conclusions.

Trial 0104 was a phase 3, double-blind, randomized trial to evaluate the safety and efficacy of isavuconazonium versus voriconazole in the treatment of invasive fungal disease caused by

Aspergillus species or other filamentous fungi.

Patients were randomized in a 1-to-1 ratio to receive either isavuconazonium or voriconazole, and were stratified at randomization by three factors: geographic location; whether or not the patient had a prior allogeneic bone marrow transplant; and whether or not the patient had an uncontrolled malignancy at baseline.

An independent data review committee that consisted of experts in the field of infectious disease was established to adjudicate the categorization of each patient's IFD at enrollment as proven, probable, possible, or no IFD, no invasive mold infection. This was based on the presence of adequate host factors, adequate radiological and clinical features, and mycological evidence from histopathology, culture and/or galactomannan. Diagnostic tests obtained within 7 days after the first administration of study drug were allowed to confirm the baseline diagnosis.

The DRC also evaluated the patient's clinical, mycological, radiological, and overall

response to treatment at the end of treatment, day 42, and day 84. The primary objective of the trial was to assess the noninferiority of isavuconazonium compared to voriconazole based on the primary endpoint of all-cause mortality through day 42. The key secondary endpoint was the DRC assessed overall response at end of treatment.

Overall response was assessed as complete, partial, stable, or failure, based on the clinical, mycological, and radiological findings. A patient with complete or partial overall response was considered a success.

Multiple analysis populations were used for the efficacy analyses, and included the intent-to-treat population, which consisted of all randomized patients who received at least one administration of study drug.

The modified intent-to-treat population consisted of ITT patients with proven or probable IFD at enrollment as determined by the DRC. In this population, patients with appropriate host factors and clinical features could be considered

to have probable invasive aspergillosis based on the galactomannan criteria of two consecutive serum galactomannan values greater than or equal to 0.5, or at least 1 serum galactomannan value greater than or equal to 0.7, as defined in the protocol.

Recently, the FDA has provided draft guidance on the qualification of the use of galactomannan in classifying the diagnosis of invasive aspergillosis for use in the enrollment of clinical trials.

It is recommended that two consecutive serum galactomannan values greater than or equal to 0.5, or at least 1 serum or 1 BAL galactomannan value greater than or equal to 1.0, be used to define a probable case of invasive aspergillosis. Therefore, the additional mITT FDA population was defined based on these criteria.

Additionally, the mycological ITT population was defined and consisted of mITT patients with proven or probable invasive aspergillosis at enrollment.

As stated, the primary objective of the

trial was to assess noninferiority of isavuconazonium compared to voriconazole and all-cause mortality through day 42. This was based on a prespecified and justified margin of 10 percent. To determine the margin, the effect that the active control voriconazole has over no treatment needs to be determined. Ideally, this would come from randomized trials of voriconazole versus placebo. However, these trials are unethical to conduct, so multiple sources of data were used to provide the information to justify the margin.

The estimate of response for voriconazole is based on the original registration trial of voriconazole, in which voriconazole was shows to be superior to amphotericin B. Based on this data, the estimate of all-cause mortality at day 42 for voriconazole was 18.8 percent, with an upper bound of the 95 percent confidence interval about this rate of 26.1 percent.

Additionally, the effect of voriconazole over amphotericin B could be as little as

5.5 percent better, as seen from the upper bound of the 95 percent confidence interval; about the difference of voriconazole minus amphotericin B.

A literature search was conducted to derive an estimate of placebo response, as well as a historical estimate of amphotericin B response. The literature search was provided by the applicant, and included publications from 1952 to 2006. The majority of these publications were case series or case reports, and not randomized controlled trials.

The division reviewed these publications and determined cases of invasive aspergillosis, which had a pre-mortem diagnosis and similar underlying disease and patient characteristics to those of the current trial.

Based on this, we found 21 cases who received no antifungal treatment, with 100 percent mortality rate at 6 weeks, and a lower bound of the confidence interval of 83.9 percent. Additionally, 137 cases who received amphotericin B were found. The mortality rate for these amphotericin B treated

cases was approximately 60 percent.

Thus a conservative estimate of the effect of amphotericin B over placebo comes from the difference of the lower bound of the placebo rate and the upper bound of the amphotericin B rate, which is 15.8 percent in favor of amphotericin B.

We then used two approaches to get an estimate of the effect of voriconazole over placebo, or M1. The first is a direct comparison of the estimate of the voriconazole response and the placebo response, and is based on the difference of the upper bound of the estimate of all-cause mortality for voriconazole, which was 26.1 percent, and the lower bound of the placebo estimate, which was 83.9 percent. This difference is 57.8 percent in favor of voriconazole.

A highly conservative estimate of M1 comes from an indirect comparison, which is based on the effect of voriconazole over amphotericin B seen in the original registration trial of voriconazole, which was minus 5.5 percent, plus a discounted effect of the effect of amphotericin B over placebo

derived from the cases found from the literature search, which we took to be half of minus 15.8 percent.

This leads to an estimate of M1, which is approximately 13.4 percent in favor of voriconazole. Therefore, a noninferiority margin of 10 percent, based on clinical judgment for M2, is acceptable for assessing all-cause mortality through day 42.

Based on historical data available, an estimate for M1 for overall response at end of treatment cannot be derived. However, historical data suggests an estimate of M1 for overall response at week 6 is at least 20 percent.

Since the median duration of treatment in trial 0104 was 45 days, which is approximately 6 weeks, the clinical interpretive criterion of 15 percent prespecified by the applicant was determined to be acceptable for assessing overall response at end of treatment.

Overall, 527 patients were randomized into the trial. Eleven patients did not receive any

dose of study medication, therefore the ITT population consisted of 516 patients, or 258 patients in each treatment group.

Two-hundred and forty-four patients were assessed by the DRC as having either possible or no IFD at baseline, and were excluded from the mITT population. Of those included in the mITT population, most were considered to have invasive aspergillosis. The most common pathogens identified were Aspergillus fumigatus and Aspergillus flavus.

While there is only a net difference of three patients between the mITT and the mITT FDA population, the mITT/FDA population includes 20 patients who were considered probable based on a BAL galactomannan greater than or equal to 1, but excludes 17 patients who were considered probable in the mITT population based on a single serum galactomannan value between 0.7 and 1.

The myITT population consists of 123 isavuconazonium and 108 voriconazole patients with proven or probable aspergillosis, of which more

than half were considered probable based on serum galactomannan as the microbiological evidence.

Demographic and baseline characteristics of the ITT population were generally balanced among treatment groups. The mean age was 51 years, 60 percent were male and 78 percent were white. The overall distribution of geographic region was 11 percent from the United States or Canada, 41 percent from Western Europe, Australia or New Zealand, and 48 percent from all other regions. Approximately 20 percent of the patients had a prior allogenic bone marrow transplant, and 70 percent had uncontrolled malignancy at baseline.

The results for all-cause mortality through day 42 are presented here for the various analysis populations. In the ITT population, the all-cause mortality rate through day 42 was 18.6 percent for isavuconazonium and 20.2 percent for voriconazole.

The adjusted treatment difference of isavuconazonium minus voriconazole, adjusted for the stratification factors of geographic region, allogenic bone marrow transplant status, and

uncontrolled malignancy status, was minus 1 percent, with a 95 percent confidence interval of minus 8 to 5.9 percent.

Since the upper bound of the 95 percent confidence interval about the adjusted difference was less than 10 percent, noninferiority of isavuconazonium compared to voriconazole was demonstrated with respect to all-cause mortality through day 42.

The results are robust across the various analysis populations where the adjusted treatment differences of the remaining analysis populations ranged from minus 2.7 percent to minus 2.1 percent, and the upper bounds of the 95 percent confidence intervals about the adjusted difference ranged from 7.3 to 8.2 percent, which are all less than the 10 percent noninferiority margin.

CRC assessed overall response rates at end of treatment in the mITT population were similar between treatment groups, and was 35 percent for isavuconazonium and 36.4 percent for voriconazole. The lower bound of the 95 percent confidence

interval about the adjusted treatment difference, which was calculated as isavuconazonium minus voriconazole, was minus 12.8 percent.

The results for the mITT FDA population were similar, as were the results for the myITT population, although there was a slightly higher DRC assessed overall response observed for voriconazole patients in the myITT population.

In conclusion, noninferiority of isavuconazonium compared to voriconazole, based on a 10 percent margin, was demonstrated for all-cause mortality through day 42. And similar rates of DRC assessed overall response at end of treatment were observed between the treatment groups.

I will now turn the presentation over to Dr. Ed Weinstein who will present the division's assessment of the clinical efficacy of invasive mucormycosis and the overall safety of isavuconazonium.

FDA Presentation - Edward Weinstein

DR. WEINSTEIN: Hi. Good morning. My name is Ed Weinstein, and I am a clinical reviewer in

the Division of Anti-infectives, and I have a two-part talk for you today. The first portion concerns the clinical efficacy of isavuconazonium for the treatment of invasive mucormycosis, followed by a pause, a deep breath, and a discussion of the overview of safety.

So we'll start with the clinical efficacy for the treatment of isavuconazonium for the treatment of invasive mucormycosis. I'll discuss the study design, the population demographics, patient disposition, the outcomes, and a comparative analysis of the trial data with historical control populations.

So the study design has already been mentioned previously this morning, and the data for the indication come from trial 9766-CL-0103. This is a non-comparative, open label, multicenter, multinational trial that sought to recruit patients with renal impairment, with a disease of invasive aspergillosis, as well as patients with invasive fungal disease caused by rare molds, yeast, or dimorphic fungi.

So as mentioned, IV voriconazole is not recommended for treatment in patients with renal impairment, and there is no indication for voriconazole for the treatment of mucormycosis.

So 149 patients were enrolled; 146 patients received study medication. And within this population, the Data Review Committee identified 37 patients with Mucorales infection. There were 24 patients with Aspergillus infection, 20 of which had renal insufficiency.

So taking a closer look at the Mucorales population, initially, 46 patients were enrolled, however 9 were excluded, 1 with a possible infection and 8 with mixed infection. This yielded the 37. And the Data Review Committee used the European Organization for Research and Treatment of Cancer, mycoses study group criteria from 2008 to make these diagnoses.

So because we're taking 37 patients and we're applying the data to a large and heterogeneous population of patients with mucormycosis, I'm going to spend the next five

slides looking closely at how these patients compare to the epidemiologic studies. So I'll look at the diagnosis in treatment group, the population demographics, host factors, the identified pathogen, and the site of infection.

So the first way to consider this group is on the basis of the diagnosis, and they fall into two categories, proven disease, which mostly involves the recovery of evidence for the disease from an otherwise sterile site. Probable disease also involved recovery of hyphal elements, but there was also supporting data, such as clinical factors, like immunosuppression and radiographic data as well.

The treatment groups could be divided into three separate groups. The first was primary treatment, which involved patients that had not received antifungal therapy previously.

The following two categories are salvage therapy. That involved refractory patients, that is patients that progressed in their disease while undergoing antifungal therapy, and patients who

were intolerant of treatment. Those were patients such as those receiving amphotericin that developed renal failure, or patients that couldn't develop a therapeutic drug level. These designations were confirmed by the Data Review Committee.

So taking another look at the population, the mean age was about 49 years, with a range of 22 to 79. Eighty percent were males, 67 percent white, 70 percent had normal renal function, and 43 percent were found within the United States.

The underlying host factors -- this is a fairly complicated slide, which I'll walk you through. The study population is found on the left column, and then in comparison are two epidemiologic studies.

The first was a landmark study, which was done by Maureen Roden and Tom Walsh back in 2005. They managed to accumulate 929 cases of mucormycosis dating back over 100 years. There was another study though that was done in Europe by Skiada between 2005 and 2007, looking at 230 patients.

What you see is that the typical patient with mucormycosis has evolved over time. And what you see is from the larger study, there are more patients with burn, trauma, even no underlying disease, and diabetics, and this has shifted over time to more patients now, as a result of medical care and evolving medical knowledge, to the patients with hematologic malignancy, and neutropenia at baseline.

If you consider the study population, these are relatively now sicker patients. There's a higher proportion of patients with hematologic malignancy, and a higher proportion of patients with neutropenia at baseline. So these are patients that would be expected to do worse than the historical controls.

If you take a look at the microbes that were identified within the 37 patients, it's pretty much as you'd expect to the epidemiologic record, Mucor and Rhizopus were the most commonly recovered organisms. Because we only have 37 patients, some Mucorales were under-represented.

One example is Cunninghamella. And so Roden's study identified Cunninghamella as an organism with a slightly worse outcome, and so there's only one example of that particular pathogen, and this is a limitation to bear in mind.

In terms of the site of infections, this is very important in terms of the outcomes. So patients who have disseminated disease or CNS involvement have a higher rate of mortality. If you look at the study population on the left and then you compare it to the control populations, looking at Roden first, what you see is there's more skin involvement, which has a better outcome, and there is less CNS involvement.

The right-most column is Chamilos et al. And this was a modern study that was done in Texas between 1989 and 2006 at MD Anderson. And what you see is that within the study population, there's relatively more patients with disseminated disease, and more patients with CNS disease. So again, this is a sicker population that you would expect to have a worse outcome.

Next, we'll consider the patient disposition. Approximately one-third of the patients completed therapy, two-thirds discontinued. The reasons were pretty much as expected. Thirty percent succumbed to their illness, 16 percent had an adverse event or intercurrent illness. That would be things like bacteremia or relapse of their underlying malignancy. Two patients had ongoing treatment at the time of data lock.

So the outcomes really fell into two different categories that have been discussed previously. There was the Data Review Committee assessment, and this was initially the primary outcome. However, it became difficult to compare this data to the historical record, and so all-cause mortality at day 42 and 84 became the primary outcome at the time of application.

So looking at this primary outcome, and stratifying it by two different lengths of time, looking at day 42 and then the right-most column incorporating all of the patients, all 37,

mortality at day 42 was 37.8 percent, and this was consistent across the different treatment groups. If you extend the window of observation and treatment longer, there was higher mortality, which is expected, 43.2 percent, which again remained consistent across the treatment groups.

We next looked at the DRC assessed overall response at the end of therapy, and one-third of the patients were deemed to be a success. This was on the basis of clinical mycologic and radiographic criteria.

Within the designated failure group, as said previously, 28 percent were considered stable, and that's not insignificant considering mucormycosis is a highly lethal and rapidly progressive disease. Two patients were not assessed due to ongoing treatment.

Next, this brings us to our analysis strategy for efficacy. Amphotericin B is the only FDA approved drug for invasive mucormycosis. A justification of the noninferiority margin for amphotericin B was not established, so we've

concentrated on the benefit of isavuconazonium relative to no treatment at all, or the natural history.

This brings us back to these epidemiologic studies that I had just cited. Roden was the landmark one, and 96.7 percent were estimated to have expired without treatment. Skiada presented a similar point estimate of 95.5 percent, and the Fungiscope presented 29 patients who did not receive treatment with 100 percent mortality.

The meta-analysis that was provided by the applicant suggested a point estimate of 96.2 percent with a confidence interval of 94 percent to 98.4 percent. There are some major limitations to this data, the caveats that need to be described.

The first is that there was a large number of post-mortem diagnoses. And you can imagine that if you start off with a patient at diagnosis who's expired, their chances for reanimation are quite low, so this is going to overestimate death.

Other small caveats include the fact that

the site of infection, the length of time for follow-up, are these patients being followed for one month or for a year, are not well-established; underlying host factors as well.

There was one study, however, that we did identify that we thought was informative. And this was a study that was done by Dimitrios Kontoyiannis at MD Anderson, and I alluded to it earlier. He was asking the question of what's a meaningful clinical delay in treatment, and he approached it from that perspective.

His group accumulated 70 consecutive patients with hematologic malignancy with mucormycosis between 1989 and 2006. And what they were looking for was to see what would happen if they did a statistical breakpoint of 6 days, so patients who were treated with amphotericin B based therapy within the first 6 days versus patients for which there was a delay of greater than 6 days followed by amphotericin B therapy.

They used the same diagnostic criteria as the study; so it was the EORTC/MSG criteria. Their

demographics appear to be roughly similar, 64 percent male, about 50 years of age. Sites of infection were relatively well matched, and the species were also relatively well matched. And the observation period was 84 days, same as within the study.

So the outcome of delaying amphotericin B based therapy resulted in a twofold increase in mortality at 84 days, compared with early treatment, 82.9 percent just delaying 6 days. This is not no treatment, this is conservative. This is just a delay of treatment of 6 days, of at least 6 days.

So trying to put this together into a context that would then make analytic sense, I've got another complicated slide for you. On the right, we have the untreated patients in the Mucor meta-analysis. That's 96.2 percent with a range of 94 to 98.4 percent.

On the left-most column, we have the isavuconazole treated patients, all 37 of them. Day 42 mortality was 37.8 percent; day 84 mortality

was 43.2 percent. Now within bold is the most direct comparison that was available from the existing data.

This is primary therapy, isavuconazole treated patients, 42.9 percent survival, with a range of 21.8 to 66 percent. This compares to the Chamilos data of an 82.9 percent mortality, with a range of 68.9 percent to 96.8 percent with a delay of therapy.

The confidence intervals do not overlap. This suggests that there is evidence for efficacy of isavuconazonium treatment relative at least to a 6-day delay of treatment with amphotericin B, and by extension to no treatment at all.

The points of discussion that we'd really appreciate to hear from our advisors are, first of all, whether the historical data adequately supports efficacy; and secondly, how well did these 37 patients represent the heterogeneous and broad population of patients with mucormycosis?

So I'll move on to the overview of clinical safety. I'll discuss 9 clinical safety results, a

summary of drug exposure, the major safety results, common AEs, submission specific AEs, and some drug class associated AEs of interest.

So from the non-clinical toxicology data, there were some significant liver findings. There was reversible increases in liver weights in mice, rats and monkeys. There was no morphological evidence for hepatocellular damage. And like many other triazoles, isavuconazole induced CYP3A and/or CPYP2B. Within the adrenals, there are reversible increase in adrenal weights and/or vacuolation/hypertrophy in the adrenal corticol cells of monkeys.

There were significant embryo fetal developmental findings. There were skeletal abnormalities in rats and rabbits at one-tenth the human equivalent to systemic exposure.

There was increased rat pup perinatal mortality at one-half the human equivalent systemic exposure. And finally the drug was detected in milk of lactating dams at concentrations of up to 17-fold higher than plasma.

In terms of the overall development program as noted previously, there was extensive exposure, over 1600 patients, and what I wish to draw your attention to is the fact that renally-impaired subjects were assessed, including patients on dialysis, hepatically-impaired patients with mild to moderate impairment.

Within this group the exposure ranges went as high as 600 milligrams for a single dose, 1600 milligrams for a loading dose. There are instances in which patients had been exposed to over 800 days of therapy.

Within bold is the primary group to consider for the safety analysis. This was the comparative trial for the indication of invasive aspergillosis. And we'll take a closer look at the exposure within this population. This is a Kaplan-Meier curve incorporating both oral and IV exposure, and the two arms are nearly superimposed. This is a correction from the briefing document, and only IV exposure was demonstrated.

The first safety consideration is deaths.

There is a similar number of deaths within the two treatment arms. It could be subdivided into a number of different strata. If you look at all of the deaths that were known to occur, it remains balanced. Looking within bold, these are the deaths that occurred within a treatment emergent adverse event.

You could extend further to deaths that occurred with an AE onset that was reported prior to treatment, this would be things like relapse of malignancy. And there were some deaths that were reported 28 days after the end of therapy, for which there were no AEs.

So taking a closer look at those deaths in bold, the treatment emergent adverse events that led to death. So the absolute number is slightly lower within the isavuconazonium treatment arm, but remains relatively balanced in terms of the frequency and distribution of causes.

I've highlighted the three most common causes, and these are pretty much as expected. Infections include progression of the fungal

infection, as well as bacteremias. The pulmonary system was often a target of disease, both for underlying malignancy as well as for the fungal infection, and so that's the second most common cause of deaths. And this is a patient population with a significant number of hematologic malignancies, so neoplasms were the third most common cause of death.

Looking at serious adverse events, again there is a fairly good balance in terms of the frequency and distribution of serious adverse events, the absolute number of events was lower in the isavuconazonium treatment arm. The most frequent events at the preferred term level are respiratory failure, septic shock, febrile neutropenia, fever, sepsis, renal failure, pneumonia, AML, and multi-organ failure.

In terms of the absolute number, they were lower in the isavuconazonium treatment arm relative to voriconazole with the exception of febrile neutropenia. I think this just highlights that this is a sick underlying patient because something

like febrile neutropenia would be more associated with the underlying host condition than the drug administration.

Discontinuations. There are fewer isavuconazonium-treated patients who discontinued than voriconazole-treated patients. And there are some notable differences that had been highlighted in earlier presentations, but this is just from the perspective of events that caused discontinuation.

So there are fewer hepatobiliary disorders that result in discontinuation, fewer skin and subcutaneous tissue disorders, and fewer psychiatric disorders. The skin and subcutaneous disorders include things like drug rashes, and psychiatric disorders include things like visual hallucinations, which are well known to occur with voriconazole.

Looking at the phase 1 healthy volunteer population, there were seven discontinuations that did occur in subjects taking super-pharmacologic doses of isavuconazonium, the 600 milligram dose. Just by reference, 200 milligrams is the daily

maintenance dose. The reasons for discontinuation included AEs of anxiety, flushing, headache, dizziness, attention disturbances, nausea, diarrhea and vomiting. A single subject could have multiple AEs that resulted in discontinuation.

The most common AEs -- and as shown previously, almost all of the patients had at least one treatment related adverse event. The most common were nausea, vomiting, diarrhea, fever, hypokalemia, headache and constipation.

Hepatotoxicity is a safety issue of concern for triazoles, and so we looked at the hepatobiliary system organ class in general. Overall, there were fewer events that occurred within the isavuconazonium treatment arm relative to voriconazole. And when subdivided by the investigator, based upon severity, there were fewer severe events within isavuconazonium relative to voriconazole.

Approximately half of the events resolved by the end of therapy, and one-third were resolving. This is in comparison to voriconazole where half of

them did resolve, but a larger proportion were ongoing at the time of end of therapy.

Looking at serious treatment adverse events, there were 3 within the isavuconazonium treatment arm, and 6 within voriconazole. Of those three, one did lead to discontinuation, and ultimately to a patient death. So let's take a closer look at the patient who died due to acute hepatic failure.

This was a 58-year-old white male with a history of large B-cell lymphoma, chronic lymphocytic leukemia, unstaged squamous cell carcinoma of the lung. He was being treated for aspergillosis fumigatus pneumonia. Drug was discontinued on day 4 due to acute hepatitis that was reported on day 5. On days 5 and 6, ALT and AST rose above 5 times the upper limit of normal.

The patient died on day 6 due to septic shock according to the investigator; however blood cultures were not positive. Hepatitis serology was not available, and autopsy was not performed. Concomitant medications included acetaminophen that was administered under a hospital setting. The

patient did not have a bilirubin value drawn, and as such, did not qualify as part of the list of subjects that satisfied the lab criteria for Hy's law. So the role of isavuconazole can't be excluded in this patient's acute hepatic end failure and death, and there isn't a ready alternative etiology.

There was a second patient who also suffered acute hepatic failure and death in the second trial, 9766-C-0103. This was a 28-year-old white male with a history of chronic hep C, relapsed acute myelogenous leukemia status plus a bone marrow transplant on day 223, complicated by a grade 3 graft versus host disease.

He was being treated for Rhizomucor pusillus pneumonia with isavuconazonium. Treatment was discontinued on day 18 due to acute hepatic failure. The patient died from multi-organ failure five days later with progression of pneumonia despite surgical intervention and ongoing hepatic failure.

The possible causes include activation of

his chronic hep C, sepsis, AML progression, graft versus host disease, and multiple drug toxicities. This patient did qualify for the criteria that satisfied Hy's law. The role of isavuconazole can't be excluded in this patient's hepatic failure and death, but there are multiple other etiologies that that could be considered.

Looking at the laboratory investigations involved with hepatotoxicity, there are overall fewer laboratory abnormalities involved with isavuconazonium treatment relative to voriconazole. There were 3 patients who satisfied the lab criteria for Hy's law in the isavuconazonium treatment arm, and 7 in the voriconazole treatment arm.

An application specific concern, which has already been raised, is the presence of particulate within the intravenous formulation. It's there as a part of the manufacturing process, and further particulate can be formed. As the drug sits within the infusion bag, there is some spontaneous hydrolysis that does occur. A total of 27 subjects

received isavuconazonium without a filter. There were no thromboembolic adverse events that were associated with the administration.

We then looked at a broader survey of adverse events that could be potentially related to infusion of particulate drug material. This included surveys for pulmonary embolism, narrow standardized medical queries, thromboembolic and thrombotic events, pulmonary hypertension, endocarditis and infusion site reactions. And there was no significant signal that was observed relative to voriconazole intravenous administration.

Another safety finding that is fairly unique to isavuconazonium that had already been mentioned was QT segment shortening. There were two Thorough QT studies that were done. Azoles or triazoles are typically associated with prolonged QT. The studies did not show prolongation of QT, but in fact showed shortening of the QT.

There's really no scientific consensus as to what a significant shortening of the QT might

entail, but there were some data that were generated from the trial that would be of interest. In terms of the absolute QTc interval that was collected on serial 12-lead EKGs, there were instances that were balanced between isavuconazonium and voriconazole of an interval being less than 330 milliseconds.

Some authors cite 330 milliseconds as having probable possibility for familial short QT syndrome; however the diagnosis is far more complicated than just a reading of a QT segment alone. Those diagnostic criteria are also not well established.

There was one patient who had a QT segment that was less than 300 milliseconds. There was one patient who had a short QT listed as an adverse event. There were no sequelae associated with that one patient, no cardiac sequelae.

In terms of the absolute decrease in the QT interval, there were more patients who had a decrease of greater than 60 milliseconds for isavuconazonium treatment versus fewer, 10 patients

in the voriconazole treatment arm.

Hypersensitivity reactions are well known to occur with triazole antifungals. And while there was no overt hypersensitivity reactions, there were certainly some evidence to support that hypersensitivity reactions could occur in this drug as well. So I've collected three particular examples.

One is a patient who experienced an SAE listed as dyspnea that occurred during infusion. The patient improved with both diuresis and steroids. The study drug was stopped and not reinstated. It's reasonable to consider that hypersensitivity was the possible etiology of this severe adverse event.

There was another patient who discontinued IV isavuconazonium on study day 2 due to AE of allergic dermatitis that was treated with steroids. The investigator considered the reaction probably related to isavuconazonium.

Finally, there was a patient who discontinued isavuconazonium due to severe chills

and rigors on infusion day 11. The adverse reaction reoccurred on re-challenge the very next day. Vital signs were unremarkable, however isavuconazonium was permanently discontinued.

So the next sort of class-specific adverse reaction of interest would be infusion reactions, which are well known to occur with other triazoles So we looked at the number and percentage of patients with an AE that occurred within two days of IV dosing that led to discontinuation. And there were 8 patients in the isavuconazonium treatment arm and 6 within the voriconazole treatment arm, so it's relatively balanced. And the events included acute respiratory failure, chills, convulsions, dyspnea, epilepsy, hypertension, and respiratory distress.

So overall in terms of the safety summary from the comparative phase 3 trial, the patients in the isavuconazonium arm generally experienced a similar frequency and causes of death. The absolute number was slightly lower in the isavuconazonium treatment arm. A similar frequency

and distribution of serious adverse events, although the absolute number was again slightly lower in the isavuconazonium treatment arm. There were fewer events that led to study drug discontinuation.

The profile of the adverse events is consistent with a drug in the triazole class, with evidence for hepatotoxicity and hypersensitivity reactions. The safety concerns that are unique to isavuconazonium include QT segment shortening of uncertain clinical significance, and particulate within the intravenous formulation. So overall, the safety profile of isavuconazonium is favorable as compares to voriconazole.

So I'd like to acknowledge the hard work of the review team, and thank you to my colleagues to coming for the talk today.

Clarifying Questions

DR. MOORE: Thank you, Dr. Weinstein.

We'll now proceed with clarifying questions. Dr. Andrews?

DR. ANDREWS: I have a couple of questions.

One is, can somebody talk about the fetal abnormality and nursing? That seems very high to me. And I'm not a clinician, and this isn't my area of science, but that seems really disturbing and whether this is a safe drug for pregnant and nursing women and for children.

My second question is these drugs look great. I mean they keep people from 100 percent death, and that's a good thing, but they still have a very high death rate, but I understand this is among people who are not well to start with.

Is there any data or best guess of what the mortality rate is for people with these sorts of conditions who don't have an infection? Because the infection rate, the successfully treating the infection rate is only about a third. So I'm not understanding how that works.

I wasn't clear. You're confused.

DR. WEINSTEIN: Thank you for the questions. And the first question, as I understand it, is a commentary on the skeletal fetal developmental findings. And similar to other azoles, there are

known toxicities to the fetus that includes an increased risk of death, which is serious. Other triazole antifungals do contain warnings, and it's considered that these findings are not different than other triazole antifungals. So it would be considered to be a high-risk drug for a patient who would be pregnant.

The second question that you had asked was the relative benefit of 30 percent survival. And this is actually something that I was really hoping that the committee would comment on. So the relative benefit of 30 percent survival versus a condition which is nearly uniformly fatal. So I would defer on responding to that, to the second question.

DR. ANDREWS: I obviously don't have the answer. But the question is, are other drugs in this class also -- are there limitations around children, and not just fetal development, but also for children?

DR. ALEXANDER: So I think in terms of the concerns with regards to the skeletal

abnormalities, that is a sort of a limitation that's present in these other drugs, so voriconazole, itraconazole as well. And Wendy, if you want to speak up to the specific issues with regards to the pharm/tox findings.

DR. SCHMIDT: I'm Wendelyn Schmidt. I'm the pharm/tox team leader for this compound. The drugs in the fetal -- or the abnormalities in the fetal studies, that's where you're basically giving the drug to pregnant rats and rabbits during the period of gestational development -- organogenesis. Excuse me.

There you're finding abnormalities in skeletal formation. It's usually things like missing ribs, wavy ribs in these cases. It is a class effect. It is not just isavuconazole. It's also voriconazole and itraconazole. So this is nothing -- it really is not an effect you're seeing after fetal development, it is strictly during fetal development. So it's not a concern as much for children.

Now, there were some findings of increased

deaths if you keep feeding the mothers and they're breastfeeding, basically, the pups. So you're still having some increased deaths there. So that would contraindicate nursing. But again, it's a class effect; it's not peculiar to this particular drug.

DR. ALEXANDER: So the skeletal findings are something that we think affects the issue of use during pregnancy. For voriconazole, there is labeling in children aged 12 years of age and older, just on the basis of what's been studied thus far and the data that we have available. I do think that it is used off-label in children that are younger than that, and the issue of studying children with this isavuconazonium product is something that we still have yet to address with the sponsor.

DR. MOORE: All right, we're going to go to Dr. Bennett. He has a question. Is he on the phone? Do we have Dr. Bennett?

DR. BENNETT: Can you hear me now?

DR. MOORE: I can hear you now, Dr. Bennett.

DR. BENNETT: Good. I have a comment and a question about the data on mucormycosis. When you're treating a patient who is immunocompromised, with mucormycosis, using amphotericin B, it's obvious that the effects of the amphotericin B is much less important than the course of the immunosuppression during treatment, is how far off is the neutrophil coming, is it rising rapidly? What are the other immunocompromising conditions? Is a dose of methylprednisolone going down, et cetera?

So when you're trying -- this enormous heterogeneity during treatment must be very difficult to capture on a case report form, or a Fungiscope document. So I'm asking the FDA, when they went back to review the case, were they really satisfied that the matching -- this is a very tiny number of cases in the beginning, but were they satisfied with the matching process?

The second has to do with evidence of activity of the original infection when you're using it as salvage therapy. Was it the patients

were intolerant or failing? Because you need to know that the original drug treatment was ineffective, and that judgment is difficult to make. Often it's made on imaging studies, which lag behind the clinical response.

So the imaging of the sinuses or of the lung may not show improvement, yet the patient's getting better. And the original drug is responsible for the improvement, not the isavuconazole that's added on later. So the second question for the FDA is when you're talking about response in salvage therapy, were you convinced that it was due to the isavuconazole and not the original drug? Thank you.

DR. WEINSTEIN: Thank you very much, Dr. Bennett, for those questions. We do share your concerns. The first concern was about the adequacy of matching between the mucormycosis patient population and the Fungiscope patients. There was a limited number of patients within the Fungiscope, and so my understanding is only the most pertinent variables were selected.

But you're absolutely correct, there's a protean number of variables, including the neutrophil level, as it varies over time is just one of several. So only a few of the variables were captured in that comparison. We did not put a tremendous amount of weight in our analyses on the results of the Fungiscope database.

The second question that you asked, I felt was also very excellent, and thank you for asking it. The criteria that went into the composite score for the Data Review Committee included imaging data. And imaging data is notoriously a lagging indicator because you're talking about anatomic changes. There were criteria within the charter, such as changes from baseline, but that isn't always a concern with imaging, because it reflects anatomic changes.

Second was mycologic criteria I think you had raised. It's easy to first prove the presence of a disease, but then it becomes much more problematic to prove its absence because you're reliant upon accurate sampling. So thank you very

much for those criticisms, and we absolutely do agree with you.

DR. BENNETT: Thank you.

DR. MOORE: Dr. Shyr?

DR. SHYR: First question is for Dr. Dixon. Can we move to the slide 6 of her presentation please? I have questions. If you looked at amphotericin B for those two tables, the mortality rates are such a huge difference, 60 percent versus 34.6 versus 59.9. Do you have any explanation, the reason why these two statistics look so different?

DR. DIXON: The data from the voriconazole trial is more --

DR. SHYR: Healthier?

DR. DIXON: Well not healthier, it's more of a current trial and information, whereas the data from the historical literature review does consist of older -- patients that are found further in the past, where diagnosis and treatment availability for the underlying conditions was not as good as it is today.

DR. SHYR: So there are some baseline

balance. Is that the case, or just purely this is a current trial, that is already -- you reviewed this for the last 40 years? Is that case --

DR. DIXON: I think the major part is that the current treatments for the underlying conditions are a lot better today that will also impact the results that are seen for the most current trial.

DR. SHYR: Okay. So that's my question.

The second question is for Dr. Weinstein. Can we move to the slide 17 for his presentation? Here you find interesting things, the 6-day delay. Have you ever tried -- is there any trend effect, 5 days, 6 days, 7 days? Do you see any of those effects there?

DR. WEINSTEIN: That's a wonderful question. Thank you very much for asking it. We were interested in the same question, and so we directly corresponded with Dimitrios Kontoyiannis trying to obtain subject level data, and unfortunately it was not available. We only have this one cut point.

DR. SHYR: Okay. My final question is, this

is crucial for this 103 trial, is how you determine those match the 33 cases. Does the FDA a hundred percent agree with the applicant's assessment of those 33 controls?

DR. WEINSTEIN: So the question is how well do we agree with the matching, and this is an echo of Dr. Bennett's question, and we do not believe that the 33 incorporate all of the variables. It's the best available data.

So we were hesitant to put a lot of weight on the Fungiscope database for several reasons. The first was that there were similar point estimates, but the confidence intervals were very wide. If there was clear superiority, that would have been more compelling.

DR. SHYR: Okay. Have you ever done any sensitivity analysis to look at that database to see how that varied?

DR. WEINSTEIN: So I would defer the answer of that question to the applicant.

DR. SHYR: All right.

DR. MOORE: Dr. Neely?

DR. NEELY: Just a quick clarification please. On table 6, which is also I think slide 11, I believe there's an error in the numbers.

To be a success, you have to a complete or partial response. So in the voriconazole arm you have 47 out of 129 there in column 2, first row, but 12 plus 34 is not equal to 47, so there's one missing somewhere.

DR. DIXON: I'll have to double check my numbers, but more than likely, yes, that is probably just a typo in the top.

DR. NEELY: And do you have a sense of which one? Is it the percentages are correct and the numbers are wrong or vice a versa? Or I guess you'll check and maybe get back to us.

DR. DIXON: The percentages are correct.

DR. NEELY: Okay. So then we can probably figure out which one is missing.

DR. MOORE: Right. Dr. Scheetz?

DR. SCHEETZ: My question is to the FDA representatives in general about where the bar is

for approval for some of these rare indications. As was pointed out earlier, there are rare conditions, and there are rare conditions that are even more rare. So specifically thinking about mucormycosis, the analysis compared to placebo is helpful, but that doesn't help me as a clinician trying to decide between the standard of care.

Also comparing to the standard of care with the 6-day delay is helpful, but it still doesn't help me decide at that day when I would start therapy, should I start amphotericin, a liposomal amphotericin product, or potentially this product.

So my question is, really, how sure do we have to be about the noninferiority of this product compared to the standard of care when given appropriately?

DR. ALEXANDER: The bar in terms of trying to assess this is actually the idea that there's substantial evidence of the efficacy and safety, and it's not necessarily a relative standard to other products.

So the bar should be on whether there's

enough evidence that this product has some evidence of efficacy over what would be expected for a placebo or an untreated patient in a similar condition.

I understand the questions about, you know, what should I choose to use. Should I use this versus use of amphotericin, but that we certainly don't have data on, and that's not part of the standard of evidence for deciding whether a product should be approved or not.

DR. MOORE: Dr. Follmann?

DR. FOLLMANN: I guess my question ties into the comment you just made, and I guess I'll begin my comment by if you could dial up slide 17 once again. And you ask at what level of evidence does this give us I guess related to approval. This is just a comparison of rates in the 0103 study in the selected patients who had mucormycosis, versus the 6-day delay group who didn't get -- who had delayed therapy.

This isn't a randomized study, and you're just comparing the rates directly. A more

sophisticated thing would be to do say propensity score methods or regression based methods to try and level the playing field in terms of known imbalances between 0103 and the patients in Chamilos, including like whether there was lung involvement and maybe hematologic malignancies and so on.

So even if we do that analysis and it still shows like, wow, this drug is great compared to delayed therapy, which is a proxy for placebo, I echo Dr. Scheetz question, is that's sort of the relevant question.

To me, really the study that we would like to do would be to compare isoconazole to amphotericin in these patients in a noninferiority study. That is really completely absent in the FDA's presentation, for good reasons. You know the study wasn't done, and all we have for that study that I'm interested in is sort of the Fungiscope match case control comparison, which is kind of questionable, weak and small numbers and all of that.

I'm wrestling with a study that I would like done and is not really done in any good fashion. I just don't see how this comparison with delayed therapy as a proxy for placebo showing maybe you know great effect, how that is relevant. And you're saying that in fact it is like still a relevant question if we knew this drug beat placebo. If we had done a placebo-controlled trial here in isoconazole one, then that would be enough for licensure.

So I guess that's just a comment that I'm wrestling with, and the FDA I guess made their point that, yes, if you would have done a placebo-controlled study of isoconazole in patients like this, who'd be happy to approve it?

DR. WEINSTEIN: So thank you, Dr. Follmann. I agree with your comments. There's always the desire of the perfect study versus the study that's feasible and the study that you have. For an incredibly rare disease that's roughly one in million, trying to get adequate patient samples to do a controlled trial might be impractical. But I

think that's for our applicant to comment upon.

DR. FOLLMANN: I had one more question as well. On slide 32, you said that 27 percent of the patients that received drug without a filter, there's about a 7 percent kind of failure rate for something I assume is you know an important part of drug delivery. And if you have such a high failure rate in these trials, where you're on top of everything, more or less, we might expect it to be greater in the field, you know when it's given out there.

So I wondered why is it the failure rate is so high, and why wouldn't we be concerned it would be even greater if this drug is approved?

DR. MOORE: That would, I presume, is going to be a question of the sponsor.

DR. FOLLMANN: I guess it is. I guess it would be. It was the FDA who brought up the point, but really it falls more naturally to the sponsor.

DR. MOORE: That's fine. Sponsor, you want to take that?

DR. ZEIHER: So it sounds like there were

two questions for us, and let me first comment on the feasibility. As was mentioned, trying to do a head-to-head noninferiority study in mucormycosis, we estimated would require -- again, looking at all-cause mortality as a primary endpoint, and if you powered based on assumed 40 percent mortality, somewhere in the 33 to 40 percent mortality, our estimate was it would require 800 patients.

You'll recognize our trial over the time period that it was conducted, we were able to recruit 37 patients. So trying to conduct that trial would be logistically almost impossible, at least within decades.

The other probably key issue, which is a challenge, is that the only approved therapy is amphotericin B deoxycholate, which physicians typically wouldn't use nowadays, at least European guidelines -- there aren't any U.S. guideline. But they would use a lipid formulation, which also kind of makes it a bit challenging.

Then the other challenge is what do you do when the patients develop toxicity, and you'd have

to standardize that? Most physicians would probably need to do amphotericin, probably switching potentially to something else as salvage therapy, like posaconazole. So trying to logistically do that trial would be -- from a time and duration and a high unmet medical need, would be extremely challenging.

Then the other piece is what's the standard of care, which may vary, particularly if you start to have some people who might have baseline renal insufficiency or have other things with the control arm.

Then your other question really relates to the filter, and some of the safeguards that were instituted. So we did have, as was mentioned, 27 patients who did not receive a filter. We did an investigation that was largely outside the U.S. Israel was where we saw most of the issues. It seemed to be more of a site-specific issue. And then what we did is we instituted some training, ensured that sites who maybe don't automatically have inline filters, that they had them.

Our assessments in most U.S. hospitals, inline filters are pretty standard, particularly for critically ill patients like this. In addition to that, we intend to include labeling. And then also, one other additional thing that we've also discussed with the agency is to have a label that when the drug is prepared, that the pharmacist could then take off and put onto the IV bag, indicating that an inline filter is to be used. So those were some of the precautionary measures.

I think in addition, again, going back to our assessments of the safety, if they didn't use it, we actually think -- we did not see any untoward safety effects. Our preclinical specie studies didn't involve a filter. We didn't see any embolic events or any other things. And then the safety assessments that we did, as well as what the FDA did, didn't identify any unique safety findings in those patients. It's probably because the small amount of isavuconazole that gets in, gets rapidly dissolved because we've done assessments and it rapidly dissolves in either blood or plasma.

DR. MOORE: Yes, Dr. Chiller?

DR. CHILLER: Just a couple quick questions about the mucormycosis. Obviously, there were about -- it looked like about 7 or 8 -- well maybe 7 species identified, or at least -- and some were obviously not speciated it looked like. We know that there are a tremendous amount of emerging mucormycoses causative agents. And even though, I think the top 2 or 3 remain relatively the top 2 or 3, there is some upward movement from some of the lesser species.

So I'm wondering, number 1, just from an FDA standpoint, you're going to give an indication for mucormycosis, which probably consists of hundreds of species actually, and some are not clinically relevant today, but they will be next year. And so I'm curious, but just like we've heard, to be able to identify clinical cases, and then actually identify species, is super-duper challenging.

But you can at least look at some of these in vitro, and I know that that's -- so I'm wondering -- I don't know if I saw how many species

were tested in vitro against this drug. And then that sort of relates to those that were tested in vitro that actually have in vivo data, like in the Aspergillus arm, was MIC used to look at outcome, at least in these 20 or 30 or so patients with mucormycosis?

DR. BALA: I'm Shukal Bala, the microbiology reviewer for this application. In vitro data was available. There were different sources of data. One was surveillance studies were done in 2011 and 2012. Then the applicant compiled data from the published studies, so that's listed as database. And then the clinical trial isolates. And there's a table 1 in the briefing document, the FDA briefing document, which lists the MICs from these different sources.

From the surveillance studies, the number of isolates tested were very, very small, 1 to 4 depending on the species. From the database, there was some numbers. Like for Lichthelmia, there was 6 to 7 isolates which were available, and the MIC90 was 8. And likewise for the Mucor species, there

were about 68 isolates, but MIC90 was 16.

So the MIC in general vary from 2 to 32 for these different Mucorales genera and species.

From the clinical trial isolates, again it's the same pattern. As you heard, there were 37 patients, and again different species. So when you start looking at the numbers, MICs against different species, it's within the same range.

Only one strain of Rhizopus oryzae was tested in animal model, and the MIC I believe was -- I can give you the MIC number. I don't have it here, but I can get back to you. It was within I think 4 micrograms per mL, if I remember right. So only one strain was tested in animal models. And there is activity weighted with the experimental conditions.

DR. CHILLER: Thanks. Obviously, I know there are no break points for these, but, obviously, MIC data is useful. I guess on another subject, with amphotericin B, we've heard that -- I mean, I think all of us who treat these patients are not going to use deoxycholate for the most

part; we're going to use lipid amphotericin. And I'm just curious, on the amphotericin analysis that you guys have done -- I know that we're not looking at it against ampho in this particular setting, but there were 37, 39 percent. I can't remember, was the mortality.

Has anyone broken that down between deoxycholate and lipid? Because, obviously, a lot of the old Walsh data and stuff like that would have been deoxycholate, or at least some of it going back a hundred years would be. Is there a difference between lipid and deoxycholate in any of the historical literature as far as outcomes?

DR. WEINSTEIN: So there's been numerous reports, but the problem is that they're not very well powered, and so there's certainly a collection of evidence. The only amphotericin B product that actually has the indication is the deoxycholate. The liposomal formulation doesn't formally have the indication on the label.

DR. MOORE: Thanks. Dr. Neely?

DR. NEELY: My question was very closely

related to Dr. Chiller's. Do you know the number, or maybe the sponsor knows, in all of the amphotericin comparators, whether it was the Fungiscope or from the -- I guess that would be the most likely -- or maybe the Skiada study, what percentage were liposomal amphotericin or another lipid form versus amphotericin deoxycholate?

DR. WEINSTEIN: So those data do exist, but I don't know the answer, but I could get it back to you.

DR. NEELY: Does the sponsor know?

DR. ZEIHER: I don't have the Skiada, but in our primary presentation, if we can go to the core slide from Dr. Ullmann. So actually, you can see some of the numbers and the mortality that was reported in the paper from Dr. Roden, and you can see some trends in terms of mortality, again uncontrolled, but this is some of the numbers in terms of what was reported in that publication.

In terms of our study, and this is the Fungiscope match analysis, there was a mix of patients who received either lipid formulations or

the deoxycholate. And for the controls, as primary therapy, 79 percent received a lipid formulation from the Fungiscope patients that were matched. So the other 21 percent received deoxycholate.

DR. MOORE: Thank you. Dr. Robinson?

DR. ROBINSON: Yes, a question for the agency on the interpretation of the toxicology results, particularly the liver weight enlargement in the setting of a drug that induces enzymes. Was there anything else in the toxicology that would suggest anything more than a simple induction effect being observed in the livers of the animals?

DR. SCHMIDT: Wend Schmidt again. As I recall the data, and I was not the primary reviewer, we primarily saw the liver weight increases in rat, but there was also some evidence in monkey as well, I believe.

The problem was that as you increase the duration of the dosing, the doses got lower, and lower and you saw less and less toxicity, because if you went too high, you'd kill off all your animals. So there was some hepatocellular

hypertrophy, but again that could have been enzyme induction in the rat. And there was also the thyroid findings in the rat, which again tend to correlate with that enzyme induction.

DR. ROBINSON: So is what you would interpret primarily as an induction effect anything toxic beyond that in the liver?

DR. SCHMIDT: No, there really wasn't.

DR. MOORE: Okay. Dr. Bennett, you had a question? Bear with me, Dr. Bennett. I'm sorry, there's a bit of a delay.

DR. BENNETT: Good. Can you hear me now?

DR. MOORE: I can hear you fine. Thank you.

DR. BENNETT: Good. I have a question about the MIC comparison between isavuconazole and itraconazole, because I have the impression they're very similar. And yet, itraconazole is a drug no one would ever use for mucormycosis. Now one may argue that MICs don't mean anything, but as long as you think they mean something, it would be interesting to know how the MIC of itraconazole compares with isavuconazole.

DR. MOORE: Good point. So we're going to hear from the FDA on this.

DR. BALA: This is Shukal Bala again. The MICs for isavuconazole were in general lower than itraconazole. They mimic more for voriconazole MICs against Aspergillus species.

DR. BENNETT: I'm sorry. The comparison with itra and -- I thought they were the same, but they're actually higher MICs for itra?

DR. MOORE: Just a moment.

DR. BALA: Just give me a moment. I'm trying to find the table here.

DR. MOORE: Perhaps the applicant has the data with regards to the comparative MICs for these organisms.

DR. ZEIHER: We can provide that after lunch. We will get that for you with the MICs.

DR. MOORE: That sounds fine.

DR. BENNETT: Thank you.

DR. BALA: For clinical trial isolates, no, itraconazole was not tested for clinical trials.

DR. MOORE: All right. So itraconazole was

not tested in clinical trials to which you're referring.

Dr. Bennett, that is now two questions we need to get back with you on, which we will probably do after the open public hearing if that's acceptable.

DR. BENNETT: Sure. Thank you.

DR. MOORE: Thank you.

DR. BALA: So I have one information here. From the database, which was compiled by the applicant, the isavuconazole MIC90 was 0.5, and itraconazole -- sorry 8. This is for Aspergillus flavus. And the itraconazole was 0.5. For A. fumigatus, the isavuconazole MIC90 was 2, whereas for itraconazole, it was 16. Then for Aspergillus niger, isavuconazole was 4, itraconazole was 1. For A. terreus, itraconazole was 2 and -- sorry. Isavuconazole was 2 and itraconazole was 1. And Aspergillus nidulans, isavuconazole was 1, itraconazole 2.

DR. MOORE: Thank you. Dr. Scheetz?

DR. SCHEETZ: It looks like it was noted in

the phase 1 healthy volunteer trials that if you gave three times the dose, you had patients that would subsequently discontinue therapy. Do we have any good data about the pharmacokinetic toxicodynamic thresholds that we might see, and how that might have any relevance to some of the drug interaction studies?

DR. CHILUKURI: Dakshina Chilukuri, clinical pharmacology reviewer at the FDA. So as part of the PK/PD clinical pharmacology review, we evaluated the relationship between the isavuconazole concentrations and the various adverse events noted in the clinical trials. And we actually did not observe any relationship between the systemic concentrations and some of the selected adverse events that we observed, that we selected. So no relationship between exposure and response, for the safety events.

DR. SCHEETZ: So do we know that in that healthy volunteer trial, were those discontinuations because of tolerability or were they because of adverse events?

DR. CHILUKURI: I'm not sure about that.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: Sorry. I'm a little chatty today. So this is a question for the FDA. Typically, we look for evidence from at least one well-controlled study, preferably with supportive evidence -- at least two would be ideal -- on the one hand. And then on the other extreme, there's the animal rule when human studies aren't possible.

So this kind of a little bit of a hybrid. We're being asked to consider whether there's substantial efficacy possibly leading to approval, based on -- I'm talking about the Mucorales indication here, for one historically-controlled, non-randomized, open label study.

So is there any sort of a precedent? Is there a draft guidance? Is there a policy in the works or one that's already published? Or has this happened before with another drug for another indication?

DR. NAMBIAR: Yes. This is Sumathi Nambiar. The statutory requirement is as you said, for

adequate and well-controlled investigations. But since FDAMA was passed in 1997, you know we can use one trial with confirmatory evidence, and that could come from phase 2 trials or in vitro or animal studies.

So with Mucorales, evident from our presentations, the approach we've taken is how do we get to an adequate and well-controlled trial, because comparison against the Fungiscope data isn't adequate because there is no noninferiority margin justified.

So our approach has been to use those historic controls as our basis for an adequate and a well-controlled trial, and you're trying to demonstrate that there is a treatment effect compared to putative placebo. It's 6 days' delay, which is a conservative estimate of the placebo. And we're able to demonstrate that there is a treatment effect.

So if you look at the regulatory definition or criteria for what is an adequate and well-controlled study, historical controls are

acceptable; certainly not preferred. It's got a lot of shortcomings, a lot of biases are introduced.

But in certain settings, and I think the regulations clearly say -- especially in conditions where the mortality is very high, it's a progressive disease, it's okay to use historic controls. And it certainly has been used in the oncology setting.

So if the answer was straightforward, I guess we wouldn't have been here today. So we are seeking your input and your thoughts would be very helpful to us.

DR. NEELY: I understand. Thank you. That's helpful.

DR. COX: And maybe just a couple more points. You asked the question have we been here before. And if you look back, it was probably about eight years ago or so, I think the original trials for caspofungin were historically controlled trials.

In the area of antifungal drugs, you will,

from time to time, looking at those applications, find historically controlled trials, reflecting the challenges of actually trying to study a drug in this area, so not surprising. I just wanted to throw that in there, too.

DR. MOORE: All right. Thank you. No more questions it looks like. So we'll now break for lunch. We'll reconvene again in this room in one hour from now, at 1:00 p.m.

Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 11:51 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:01 p.m.)

Open Public Hearing

DR. MOORE: Now, we are going to move on to the open public hearing session. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency at the open public hearing session of the advisory committee meeting today, the FDA believes that it's important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your

attendance at the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open manner, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

With that, will speaker number 1 please step

up to the podium and introduce yourself? Please state your name and organization you're representing for the record.

MR. SCHUELER: Matt Schueler on behalf of the Henry Schueler 41 & 9 Foundation, and as a father. Thank you for letting me be here. The silence of the evening is broken only by the crunch of my footsteps on the ice below. The blanket of whiteness covers the ground, the horizon illuminated by the leafless trees.

The sky is a cloudy white, illuminated by the traffic lights and local businesses surrounding the perimeter of the tree line. There are Christmas trees illuminated in the homes too, house lights ablaze as dinner approaches. I imagine the homes filled with families welcoming home for the next few weeks those who have returned from school.

I imagine moms busy in the kitchen, brothers and sisters laughing in the living room, or bickering over the TV channel. I imagine my own children in front of the fireplace in the family room, Henry, Anna and Joe, sweaty from their

winter's workout.

I see myself arriving home. The work day is a bit shorter as we wind down to our Christmas celebration as a family, awaiting the arrival of family members near and far. I imagine my arrival punctuated only by the overly affectionate greeting I get from our dog, who never ceases to be happy when I arrive home.

A greeting from my wife, a greeting shouted to my children in the living room, an unenthusiastic but normal response acknowledging my presence. We sit down to eat as a family in a relaxed and sometimes careless fashion that families do, never imagining that we would not be together.

Then it returns, the sickly reminder that all is not as I imagined, that one of us is absent, my oldest son Hank, removed from life by nature, his laughter only a distant echo. The million memories we shared is promise unfulfilled, his legacy left for us to shape and keep alive. The lights still burn for families intact, removed from

our nightmare. For them the dinner table awaits. Into the winter whiteness I walk.

Thank you for allowing me to speak. My name is Matt Schueler. I'm the father of Henry Schueler. I am here as a father and as a member of the Henry Schueler 41 & 9 Foundation. I have no affiliation with Astellas or any other pharmaceutical company.

Although it is seven years removed from my son's death, his loss is deeply felt every day. No matter what I have done or will do, my greatest accomplishment is to be Hank's dad and dad to Anna and Joe.

Cancer and its many complications follow its own rules despite a parent's best efforts. My oldest son, Hank, as he was known, received a diagnosis of ALL in November of 2006. He was 13 years old. His ALL was a very rare subtype known as hypodiploid, which occurs very rarely. Because of his prognosis, unanimous medical opinion recommendation was that he undergo a bone marrow transplantation immediately after the initial

course of chemotherapy. He did quite well. He had a great summer. He got back to playing baseball.

Unfortunately, over Labor Day, he experienced a relapse. His odds of a long-term survival decreased to 10 percent. He underwent additional chemotherapy, which wiped out his new immune system, and he eventually contracted a rare and deadly invasive fungal infection known as zygomycosis or mucormycosis at the end of September. Doctors told us that the infection present in his lungs and sinuses would likely kill him in a week or 10 days.

He underwent six surgeries in seven days, and given all the antifungals available to him at the time. They wreaked havoc on his body. He refused to quit despite the overwhelming odds against him.

After another bone marrow transfusion, after Thanksgiving at Children's Hospital of Milwaukee, the fungal infection reemerged. The infection spread to his orbital areas and slowly and cruelly took his eyesight. Our son, so full of life and

fun, was now blind, his eyes covered with patches to cover the effects of the fungus.

He was placed on a ventilator to breathe, to overcome the respiratory effects of a disease, which attacked his lungs, lungs which had never failed him on an athletic field or a playground, or anywhere a game was being played.

Without warning or chance to say goodbye, he suffered a massive cerebral hemorrhage and died on December 14th, 2007. More than 2000 people came to his wake. He left a 12-year-old sister and an 8-year-old brother who loved him, and whom he loved with all his heart. He left his parents with a broken heart. His sister wears his number 9 on the lacrosse field at the University of Michigan. His brother wears his football number 41 on the high school football field.

As a result of his death, many of our close friends, including a number of his former coaches, approached us to form a foundation to remember him and provide hope for others similarly afflicted. Hank had told my wife, Susan, after he experienced

a relapse, that he just wanted to grow up and find out why this happened to him so he could prevent it from happening to other kids.

In addition to our research at St. Jude's Children's Hospital on hypodiploid leukemia, our foundation sponsored the first U.S. based international conference on mucormycosis, chaired by Dr. Thomas Walsh, director of the Transplantation-Oncology Infectious Disease Program at Weill Cornell University Hospital.

Out of that conference came the research that formed the basis for the most comprehensive medical supplement on mucormycosis published as a supplement to the Journal of Infectious Diseases in February 2012.

Hank never quit a game early. He never quit fighting his disease. These friends who comprise our board helped instill that attitude in him when he was on the playing field and are determined to carry the fight forward in his absence. December 14th is the day that Hank died. Nothing will ever change that; however, it is also the day that

inspired the seeds of a gift of life for others.

New research and funding is needed. New drugs are needed. Nothing was more devastating than Hank's inspired fight against his leukemia then for him to contract a deadly fungal infection, and nothing was more helpless than to have such few options to fight that infection.

Hank Schueler did not die from the rare leukemia he had, Hank Schueler died from a fungal infection that not only can attack immunocompromised patients, but also organ transplant patients and diabetic patients in a disease that attacks the body and causes massive disfigurement and devastation. No person should ever experience such an end, and no parent or family member should have to live with the memories of such a disease.

Isavuconazole is a new antifungal medicine that we believe offers an important option for the therapy of mucormycosis. My son Hank had only one medicine, amphotericin B. If it damaged his kidneys, that was the price that we would need to

pay. If his kidneys were damaged, the doctors needed to adjust the dose, which would then cause his infection to progress.

Isavuconazole has successfully treated mucormycosis in patients like Hank with leukemia and bone marrow transplantation. Isavuconazole does not injure kidneys and appears to be otherwise safe. Mucormycosis needs weeks of therapy. Because the drug can be given IV and by mouth, patients such as Hank can be treated with an oral medicine that is a major advantage over the amphotericin in improving their quality of life.

After more than 50 years of only one medicine, amphotericin B for mucormycosis, we need a new antifungal agent to treat this terrible disease and save the lives of future children and adults.

Hank wanted to find out why this happened to him, so we can prevent it from happening to other kids. Help bring Hank's living wish closer to reality. Thank you for your time.

DR. MOORE: Thank you, Mr. Schueler.

Will the next speaker please step up to the podium and introduce yourself?

MR. BARTKOWSKI: My name is Andy Bartkowski. No one has paid for me to travel here from Bucks County, Pennsylvania. I would like to thank the chair for giving the opportunity to speak of my experience with mucormycosis.

I have a facial paralysis, and paralysis is caused by mucormycosis, which severed my seventh nerve. Portions of my face are numb. I cannot smile. I cannot close my eyelids. They only close on relaxation, not contraction.

In 1978, I was 20 years old, I was a type 1 diabetic, but that did not slow me down. I was active, working two jobs. A friend told me I was the happiest person she had ever met. When I wasn't at work, I was partying with my friends, or sleeping at the New Jersey shore and returning home to start the work cycle all over again.

Then one day I got a toothache. The pain became intolerable. I begged the dentist to extract it. Over the next several days, my cheek

and face swelled to the point where my right eye was swollen shut. I wound up in a Philadelphia hospital.

The doctor immediately consulted with an ENT, then removed the infection from my right sinus. Only due to the biopsy, he determined it was mucormycosis. They proceeded to administer amphotericin B and was told if I made it through the night, I would survive. At the same time, the surgeon said I would never be able to smile again for the rest of my life.

I received 50 to 60 milligrams of amphotericin B every other day. The side effects were symptoms of malaria, fevers as high as 105 degrees, sweats, nightmares, and of course phlebitis. The goal was to receive a thousand milligrams of amphotericin B, which took about 42 days in the hospital.

Since that time, I have had eight cranial facial surgeries for my eyes and face. I also had three kidney transplants due to diabetes. In 2008, when my sister's donated kidney started to fail

after 12 good years, I had venous mapping performed to see where I could receive a fistula. Unfortunately they found that my veins in my chest were calcified, and the veins in my arms were too damaged to receive dialysis, damage caused by mucormycosis treatment, back in the late 1970s.

I agreed with my vascular surgeon to connect a Gore-Tex vascular graft from the crotch of my arm to my jugular. On May 13th, 2010 I received my most recent kidney transplant. Since then, I became an amputee due to diabetes. I am unable to receive PICC lines for antibiotics due once again to damaging effects of the treatment I received for mucormycosis three decades ago.

In my 35 years of firsthand experience I learned a few things. To patients out there, I'm a diabetic, and I have been on immunosuppressants for 25 years, and I have not had one reoccurrence of mucormycosis. So you do not have to fear the mucormycosis, but you have to respect the possibilities.

To medical teams, I realize mucormycosis is

incredibly rare, but there has been a lack of awareness and knowledge about this infection. You either have it or you don't.

Lastly, my life was saved due to the medical treatment I received years ago, but that treatment has also caused lifelong harm. Patients today deserve to have treatment options. I urge you to consider patients like myself and our need for treatment options during your deliberations. Thank you.

DR. MOORE: Thank you, Mr. Bartkowski.

Our last open public hearing session speaker.

DR. WALSH: My name is Dr. Thomas Walsh. I'm a professor of medicine, pediatrics, microbiology and immunology at Weill Cornell Medical Center in New York Presbyterian Hospital, and director of the Transplantation-Oncology and Infectious Diseases program.

I will hasten to add that I had not planned to talk today. I traveled here on my own resources to be with Matt. I'm privileged to serve as the

scholar in mucormycosis of the Henry Schueler Foundation, and my intent was to, at best, be a mere substitute for Matt's eloquent presentation, and very eloquent presentation that we've also heard.

However, in talking to colleagues outside at lunch, a number have asked me to please speak, and to speak on behalf of whom I'll tell you in a moment. But in the spirit of full disclosure, many of you know I have extensive mission-driven collaborations with industry and developing new antimicrobials in both the research and consultative capacity. We work from bench to bedside in harnessing the best of antimicrobials that we can to save lives.

What lives are we talking about? I'm representing those individuals, not just associated with the foundation, but for all the voices that can't be here: Daisy, Sophie, Donald, Valerie, Michael, Roberto, Simone, Andula [ph], Maria. These are all children and young adults who have either died, or some have survived, from

mucormycosis. I could write the list long. I only have enough -- I only have a few index cards.

These are patients who did have trauma, diabetes, transplantation, solid organ, hematopoietic stem cell, leukemia, who looked for hope that they would be cured. Many of them have good prognosis, but in the process of treatment, in the process of the underlying diseases, mucormycosis emerged.

Imagine the devastation when a mother calls you up and says, "Dr. Walsh, my little boy is now in the operating room, and they want to remove his lung, his left hemidiaphragm, his left kidney, his stomach, and his left adrenal." And I said, that's almost an autopsy, that's not surgery. And that's how extensive this mucormycosis exploded.

I could go on and on of the multiple disfiguring surgical interventions that have been necessary for all of these children and young adults, and realizing that our therapeutic armamentarium, and our diagnostic capabilities, are extremely limited in what really is an orphan,

truly an orphan disease.

So I echo their suffering, their pains, their aspirations that we may be able to, as a community, offer something better in diagnosis, more in treatment, and more hope so that they and others may be able to live lives in fulfillment beyond the devastating pain and suffering that they have from mucormycosis. Thank you.

DR. MOORE: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will turn its -- well, before the committee turns its attention to address the task at hand, which is the careful consideration of the data before the committee as well as the public comments, we would like to have the sponsor address Dr. Bennett's original question.

Dr. Bennett, you're and the phone are you not?

DR. BENNETT: Yes.

DR. MOORE: Perfect. Your second question

about the itraconazole and isavuconazonium MICs was addressed earlier to your satisfaction. Would that be correct?

DR. BENNETT: Yes.

DR. MOORE: Okay. All right, so let's go ahead with the sponsor's presentation.

DR. ZEIHER: Sure. Thank you. First I'd like to -- this is specific to address Dr. Bennett's question about discontinuations from study 0103, and if I could first have briefing book table 26, or BT-26. Sorry. It's BT-26. Okay.

So this slide, I believe Dr. Bennett was mentioning 9 patients who discontinued from the primary therapy group. There was, as you can see, 13 discontinuations, 6 for death. There's actually 7 others, so rather than 9, it's 7. And what I'd like to do now is to describe the outcomes of those 7 patients and what information we have on them.

So these are the seven patients. So if we look at the first -- and what's listed here in the left column is the reason for discontinuation, how many days they were on therapy, when did they die,

if they died, and then what was some our DRCs assessment of outcomes.

So the first individual who had an AE or intercurrent illness actually received 509 days, and then discontinued. That patient died on day 517, and actually the DRC assessed this individual as having complete response. And at death, there was no evidence of invasive fungal disease according to the DRC's assessment, and the patient was assessed in terms of their -- due to a malignant neoplasm progression.

Next individual. This individual received 33 days of therapy, ultimately died on day 56. That individual did switch to posaconazole after day 33, and then, as I mentioned, died. And you can see the DRC's assessments initially at the end of therapy was as a stable, which according to the classification would be a failure. And at death, the DRC assess was no evidence of IFD, and the reason for death was down as acute renal failure.

The next individual withdrew consent after receiving 106 days of therapy, so had obviously

survived past our 42/84, all related to isavuconazole therapy. He was last known alive on day 107 because that was when they withdrew consent. And the DRC assessed the patient as stable, which in this case would be, according to the classification scheme, down as a failure.

The next person withdrew consent on day 4, and then died on day 5, and what appeared to be progression. Next, 15 days of therapy, died on day 17, and again from progressive IFD. And then the next person actually was down as an insufficient therapeutic response, actually received 102 days of isavuconazole. After that time point, did switch to amphotericin and was last known alive on day 328. And then there's one other individual who basically received 2 days of therapy, and then died on day 3.

So hopefully that provides some of the information that you may have been looking for, Dr. Bennett. I think the key message is, some of these individuals who discontinued actually discontinued after having very prolonged therapy,

such as either a couple individuals with more than 100 days, and one actually had more than 500 days therapy when they discontinued.

I just want to mention, if you want more information on any individual cases, we'd be happy to provide that, things like some of the disseminated cases who had complete responses with imaging, please just let us know.

Dr. Bennett, does that address the question?

DR. BENNETT: Yes. I think it exemplifies how heterogeneous not only these patients are in terms of in terms of the pathology, but their outcome, and trying to capture a group that you could then match them for outcome is very difficult. It's such a heterogeneous group, but I think you've given me all the information that I need. Thank you.

DR. ZEIHER: Thanks. The other question we thought we'd try to address, and I discussed with the chair, related to there was a number of comments or questions around kind of the heterogeneity in terms of mucormycosis and the fact

the large number of organisms, the range of MICs and so forth. And actually I would like to ask Dr. Ibrahim if he could present -- discuss first slide MU20 and then 21.

DR. IBRAHIM: Ashraf Ibrahim, professor of medicine at UCLA School of Medicine. I have been studying mucormycosis for more than 15 years, emphasis on pathogenesis, immunotherapy, and animal models. So if I can have your attention to this slide, which basically shows that mucormycosis are caused by a variety of organisms belonging to the order of Mucorales.

These are different studies assembled from different geographical areas. The one to the left is from the commonly quoted today, Roden et al. And you can see that basically mucormycosis caused by Rhizopus is by far the most frequent cause of the disease, followed by probably Mucor.

The ones which are caused by Rhizopus are basically shown in blue. And the one to the far right is actually done by Chakrabarti, et al. and shows the causes of mucormycosis is attributed,

approximately 70 percent due to Rhizopus, followed by Apophysomyces.

In addition to Mucor and Rhizopus, you have also Apophysomyces and Lichthelmia, which seems to be reported as a second cause of the disease in Europe. So if I can have slide --

DR. ZEIHER: Put up slide MU-21.

DR. IBRAHIM: So if you look at this table, which we assembled from different studies, it actually shows on the far left the cause of mucormycosis, Rhizopus, Mucor, Lichthelmia, Apophysomyces. And then the second left column is basically telling you the attributed clinical frequency, which you can see in Rhizopus ranges anywhere between 50 to 70 percent, followed by Mucor, Lichthelmia, and Apophysomyces.

So the data, which is in the table, is assembled from different studies whereby we assessed the efficacy of different antifungals in treating the disease due to Rhizopus, Mucor, Lichthelmia, and Apophysomyces.

So ISA is being presented at the far right,

and you can see that this is the median survival times. So the numbers you're looking at are median survival time. So in ISA, the median survival time is more than 21 percent. So mice treated with ISA survive in a median time more than 21 days compared to placebo, which is 4 to 8. Amphotericin B treated, in this case either amphotericin B or liposomal amphotericin B, 15 to 19 days, and posa is 4 to 13.

We've also assessed the efficacy of ISA in a model infected with Lichthelmia. And you can see also it fares well compared to placebo. And it's a little bit comparable to amphotericin B, and it also fares well to posa.

There isn't really any data against Mucor or Apophysomyces. So the message here, ISA seems to be actually doing well against the most frequent cause of mucormycosis, Rhizopus, and also fares to be really in Lichthelmia as well.

DR. ZEIHER: Thank you. Just one other comment I'd like to make around some of this. I think there was a lot of questions about primary

therapy versus -- I think from our position, really we're looking for this to be an option. And how it's actually used in the clinic will be guided really by the clinical presentation and possibly by the species that's identified. But we'd be happy to take other questions as we go along if the committee has any.

DR. MOORE: Thank you very much. I believe the FDA had some information. Talking about Mucor reminds me of the old joke, what did the king say to the cat. Rhizopus.

DR. NAMBIAR: I think the Mucor data -- I think we're okay because the applicant has addressed it, but Dr. Schmidt wanted to correct a statement that she made earlier regarding the non-clinical studies, if that's okay with you.

DR. MOORE: Of course, that's fine.

DR. SCHMIDT: Yes. I misspoke earlier. I wanted to point out that the non-clinical liver findings that you asked about were found in mouse, rat, and monkey, and primarily consisted histopathologically of hepatocellular hypertrophy

and vacuolization. So I just wanted to clarify that point. It was not just rat. It was also monkey.

DR. MOORE: Thank you for that.

DR. DIXON: I also wanted to clarify the numbers that were in table -- that was on slide 11. The complete response should be 13 for the voriconazole.

DR. MOORE: Thank you, Dr. Dixon.

All right. I'm going to introduce Dr. Sumathi Nambiar, who will provide the charge to the committee.

Charge to Committee - Sumathi Nambiar

DR. NAMBIAR: Thank you, Dr. Moore.

Today we've discussed NDAs 207500 and 207501, isavuconazonium sulfate capsules and injection, respectively. As discussed, the applicant, Astellas Pharma, is seeking the approval of isavuconazonium for two indications, invasive aspergillosis and invasive mucormycosis.

The committee has heard presentations from the applicant, the FDA, and comments from the

speakers at the open public hearing. Based on information provided to you in the briefing documents, the presentations and discussions today, we seek your input on two questions. Both questions are voting.

The first question is, has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazonium for the proposed indication of treatment of invasive aspergillosis? A, if so, please provide any recommendations concerning labeling. And if not, what additional studies or analyses are needed?

Second question is, has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazonium for the proposed indication of treatment of mucormycosis? If so, please provide any recommendations concerning labeling. If not, what additional studies or analyses are needed? Thank you.

Questions to the Committee and Discussion

DR. MOORE: All right. So why don't we proceed now with the -- let's do this. We're going

to take the questions, go over the questions. First, before we start, let me get my mind here, do we have any clarification of the questions from Dr. Nambiar?

(No response.)

DR. MOORE: I'm going to take that as a resounding no.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why

you voted as you did if you want to.

Actually, let me just say what we really need to do is help out the FDA by providing information, explaining as much as possible your rationale behind your vote. And I would like everyone, as we go around the room, to address part A and part B of the questions. So we'll continue in this manner until all the questions have been answered or discussed.

So if there are no questions or comments concerning the wording of the question, I guess we'll now open the first question to discussion, which no additional discussion I'm going to assume. Anybody? Any discussion about the first question?

(No response.)

DR. MOORE: Okay. I guess we'll move on to the vote. If there's no further discussion on this question, we'll now begin the voting process.

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection,

the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. MOORE: Jennifer is going to cast Dr. Bennett's vote in absentia.

DR. BENNETT: Thank you.

DR. MOORE: Jack, I appreciate your being with us. I know this is not easily done, but thank you.

DR. BENNETT: Thanks.

DR. MOORE: All right, so the vote is complete. Everyone has voted. Jennifer?

DR. SHEPHERD: The vote is yes, 11; zero, no; zero abstained; zero no voting.

DR. MOORE: All right. So now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and I'd like to solicit everyone to state the reason why you voted as you did into the record. And more specifically, if you can, please address both

issues -- both portions of the question, both A and B.

Actually, can we get the question back up? Would that be possible? Perfect. Thank you.

All right. Let's start with Dr. Waterman.

DR. WATERMAN: Hi. Paige Waterman. I voted yes. I do believe that this drug provides a reasonable alternative to the current therapies that are available without additional toxicities. With regard to labeling, I would say probably what has already been proposed in terms of the use of a filter, the restrictions, not including those under the age of 18, and pregnant women.

Perhaps a similar comment on hepatotoxicity as is seen with other drugs in that class. I don't know if there's been consideration for additional caution based on ethnicity in particular those of Asian descent. And then I would offer the inclusion of something with regard to screening EKGs, maybe even as specific as additional caution depending on what the QT interval is, and/or recommendations for cardiac monitoring or telemetry

while on therapy.

DR. NEELY: This is Michael Neely. I also voted yes. And I thought this was the easier of the two decisions that we were going to be asked to make today. And we had a well-designed, controlled, randomized, placebo-controlled study to base our decisions on, so I didn't have much hesitation on this question. And I don't really have any other suggestions for the labeling than has already been stated.

DR. MOORE: Thank you. Dr. Bennett?

DR. BENNETT: The drug is adequate for treating invasive aspergillosis. And I was impressed with something we didn't talk about, which was the dose proportionality in the inter-subject variability, which I think was superior to voriconazole, and that would be good news.

I'd like to append that with a comment that therapeutic drug monitoring has become very common with posaconazole and voriconazole. We've not talked about that at all, nor has been data

presented, although the question is going to be asked very commonly is, despite the indicated dose proportionality -- there's subject variability, which is relatively small -- are we going to end up in some circumstances wanting therapeutic drug monitoring. And if so, have we any idea of what a therapeutic level might be?

I don't think this committee is going to be able to address that in the absence of data. The absence of something that we haven't really talked about. And that's all I had to say. Thank you.

DR. MOORE: Thank you. Dr. Chiller?

DR. CHILLER: Tom Chiller. I vote yes. And I think the comments that have already been said are pretty much summing up the way we're feeling. Thanks.

DR. MOORE: Mr. Byrd?

MR. BYRD: Thank you. Patient representative, Christopher Byrd. I voted yes because it is apparent to me in the presentations today that this drug alternative is highly, highly needed in the patient population. And I think it's

imperative that we move these studies along so that we can start approving this drug also for patients who are younger than 18 years old. I think there's a high, high need in that population.

I do not have any additional recommendations concerning labeling that haven't already been stated. Thank you.

DR. MOORE: Thank you. Dr. Andrews.

DR. ANDREWS: Yes, I'm Ellen Andrews, a consumer representative, and I voted yes. I think it's a valuable new tool, but a lot more research needs to be done, not just for this.

It's clearly not a super fix to the problem. There are definitely improvements in efficiency, effectiveness, and safety. This is a deadly disease with few options. It hasn't been stated, but I think it's really important that there are fewer drug interactions given; that these are people with multiple problems.

I echo Christopher's concern around children, although I would like some warnings about it, maybe not contraindicated against for children

because a tool's a tool. And for pregnant women and nursing mothers as well, I think it's a tool that needs to be there, but the warnings need to be there.

I heard around -- I'm not a clinician -- but around the QT shortening interval, that associated with cardiac events but not always clear why that was, and I think that bears more study as well. And further monitoring side effects, especially for people who, because of ethnicity, may be at higher risk of higher doses over time, and so monitoring for side effects.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: Diane Cappelletty. I also voted yes, pretty much the same comments that everybody else has had. And I guess it may be intuitive in part of the labeling, but in addition to not shaking the bag after reconstitution, but not to shake the vial during reconstitution either.

DR. MOORE: Thank you. This is Dr. Moore. The comments have already been addressed, referring to shortened QT interval and breast feeding, and I

think are reasonable labeling statements. In terms of analyses, Dr. Bennett mentioned this earlier. I think that the biggest question that's going to come up is drug monitoring. And whether that would be necessary or not is not clear, but it needs to be -- well, the question will come up, and what the response will be, I'm not sure. But other than that, comments have already been made, and I think this is a bit of slam dunk today.

Dr. Scheetz?

DR. SCHEETZ: This is Marc Sheetz. I voted yes as well. I felt like the noninferiority was met in comparison to voriconazole. Also echoing Dr. Bennett and Dr. Moore's comments, I think therapeutic drug monitoring does need to be better defined, especially in humans, both pharmacodynamics, efficacy, as well as toxicity as well, toxicodynamics.

I'm really unsure where to place the slightly higher concentrations that we see in Asian populations as well as the elderly populations. And I'm also unsure where to place the potential

drug interactions. So without knowing our floors or our ceilings really for efficacy as well as toxicity, I find it pretty difficult to understand how much is too much and how much -- or how little is too little.

One additional comment that I'll make from a pharmacist's administration standpoint, we frequently see in practice many things don't occur as they've been labeled. In one of our studies, we've even see people give piperacillin/tazobactam in as short as one or two minutes when it was supposed to be infused over a half an hour.

I am a little bit concerned about potential particulate matter that can form, so reformation of the drug from the prodrug. And I think that there is a potential for that to happen in the line after the drug has been infused. Many times those lines remain unflushed, so I would at least like to see either a warning or more data that suggests that it is in fact safe, that if you had infused drug, that it would dissolve in blood/serum.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: Yu Shyr. I vote yes. As a statistician though, when I look at the noninferiority trials, there are two top things in my mind. First one is how you determine your M1, M2. Second is the quality of the trial. Let's talk about M1, M2 first. Even though the applicant and FDA used a total quite different data to find their M1, M2, but I think 10 percent is reasonable, no doubt.

Second, I talk about quality of the data. The quality of the data, for the randomization part, I feel a little bit disappointed because it's not quite a balance. If it really stratified by the key factors, I should see -- that balance degree should be better. But nevertheless, I think overall the quality of the data is still quite good.

Always, I did my analysis, I look at all the possible sensitivity analyses. Again, I really appreciate the applicant already presented once IT data. I apply to all the other possible populations.

The worst case scenario means that we'll assume those are 5 unknown cases, 3 versus 2. We assume the totally opposite. All the good ones go to the control, and the bad one goes to the treatment. The worst scenario is still 8.89 percent, still lower than 10 percent boundary. That is the worst case scenario.

So I have no reason to think this has not met -- it does not meet the noninferiority, the margins. So overall I have no problem. This is a solid yes.

DR. MOORE: I'll just say, it is never not fun having you and Dean on the panel. It's always great. Dr. Follmann?

DR. FOLLMANN: Thanks, Tom. I voted yes. I thought this was a relatively straightforward decision to make. I thought they did a nice, well justified study, the analyses robust, the different sensitivity analyses. I won't elaborate on what Dr. Shyr said.

One point I wanted to bring up had to do with the labeling, which I think Dr. Waterman

alluded to, maybe there could be additional testing or something, because it seems to me, evidence of familial short QT syndrome, I wonder how many families will have that and it's undiagnosed. So I don't know if that's something you write down and it makes you feel good, but in fact it won't really be addressing the issue in a substantive way.

DR. MOORE: Sorry, Dr. Shyr. Did you have something?

DR. SHYR: I forgot the label. I forgot to mention, I think we do need to pay a little bit of attention to non-white population because a non-inferior margin, if you look at that particular subgroup is not really fell below 10 percent. Sure, we look at so many subgroup analyses, this may be by chance, but I do think we should pay more attention for that particular non-white group.

DR. MOORE: Thank you. All right. We can now move on to the -- I'm sorry. Sorry, we'll summarize. Let me just summarize for the transcriptionist. Yes.

In brief, it was the committee's

recommendation, unanimous recommendation, that the applicant has demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of the treatment of invasive aspergillosis.

With regard to concerns regarding labeling, concerns were mentioned regarding breast feeding, short QT syndrome, and additional studies and analyses were suggested in individuals of Asian descent, or Asian ethnicity, and in children. And certainly the issue was raised about drug monitoring moving forward. I believe that summarizes the major points. We'll move on.

DR. NEELY: Dr. Moore, also --

DR. MOORE: Yes. Sorry, Dr. Neely.

DR. NEELY: This is Dr. Neely. Also the particulate matter.

DR. MOORE: Yes. Thank you for reminding me. Yes, also the particulate matter, and with Dr. Cappelletty's comment about not shaking the vials in addition to not shaking the bags.

So with that, let's move on to the second

question. Dr. Nambiar, would you care to -- okay. So the question is has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of the treatment of mucormycosis? Are there any -- anyone want to discuss the question further?

Dr. Follmann?

DR. FOLLMANN: Yes. I wanted to I guess comment about mucormycosis. One of the things that's in the FDA document, I believe, is how this is a rare disease. They could only do a one-armed study. They have around 20 patients that are proven to have mucormycosis.

So it's helpful to try and look at other bits of evidence to support the demonstration of safety and efficacy. And I understand comparing to the Fungiscope database and also the historical database with the 6-day delay and so on.

But one of the things had to do that -- our thinking about mucormycosis is informed by the result that we had in invasive aspergillosis. And perhaps if they hadn't done that study, would we be

here today just looking at the mucormycosis data?

So the data in invasive aspergillosis helps us, I think. But as a non-clinician, it's really difficult for me to understand or quantify or do much more than, oh yeah, it worked there in a different fungus with a different comparator, voriconazole.

So do you translate or how does that support that, the indication of mucormycosis, other than it's the same drug, and it's sort of a feel-good bridge or something like that. So I don't really know how to formalize that, and I wondered -- the FDA wrote guidance or mentioned this is a supportive kind of evidence for mucormycosis, and I was wondering if they could elaborate on that a little, using invasive aspergillosis information to help inform a decision on mucormycosis.

DR. MOORE: Dr. Nambiar?

DR. NAMBIAR: I can start. Yes. Certainly the pathogens are different, but in many instances, we do use evidence or efficacy in one indication to support an approval in another indication. So even

in the world of bacteria, if you have one trial in UTI and one trial -- they're different diseases, but there's enough overlap between the types of organisms causing the infections, that we feel that one can support the other.

I guess in this instance, you know patient characteristics, certainly these are all immune compromised patients, patients who need long-term therapy. So I think those are the similarities, but certainly the organism is different. So one can, to some degree, draw some conclusions from the efficacy you found with invasive aspergillosis to support that in mucormycosis.

DR. FOLLMANN: And what about the different comparator amphotericin versus voriconazole for the two indications?

DR. NAMBIAR: I don't think that per se should be a problem.

DR. MOORE: I think one aspect for me, I think it's reasonable to infer safety of the drug from one -- regardless of how it's being studied, whether it's Mucor or aspergillosis. Just speaking

personally, it's reasonable to infer that safety would -- you can infer reasonably information obtained from the aspergillosis study regarding safety to the Mucor study, or to the treatment of patients with Mucor.

What I would like to say is if you look at the Dimitrios Kontoyiannis, MD Anderson retrospective, they actually looked at the individuals who were treated within the first 6 days after diagnosing Mucor. Their mortality rate was -- as I recall, it was less than 50 percent. It's still higher than what appeared to be true for isavuconazole, but approximately the same. And I think that to me is a very powerful finding, because, again, that was a group in which there was not a significant proportion -- or a somewhat skewed proportion of individuals in that group who had skin involvement, so those were patients who had disseminated or pulmonary involvement primarily.

Any other comments or questions, discussion about this?

(No response.)

DR. MOORE: There doesn't appear to be. Okay. So then let's move on with the vote on question number 2. Once again, please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote.

Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. MOORE: Dr. Bennett has now voted.

All right. Everyone has voted. The vote is now complete. Dr. Shepherd?

DR. SHEPHERD: The vote is 8 yes; 2 no; 1 abstain; zero no voting.

DR. MOORE: All right. So once again we will go around the table and have everyone who voted state their name, vote, and explain their

vote. Let's start with you again, Dr. Waterman.

DR. WATERMAN: Hi. Paige Waterman. So I did vote yes. I don't believe safety was the concern as was just mentioned prior to the vote. The question was more one of efficacy.

Given the availability of the comparator, I believe that we met a reasonable measure of efficacy with the data that was presented. Certainly, postmarketing surveillance becomes critical for this indication. Otherwise, I don't believe I have anything additional to add regarding labeling that wasn't said previously.

DR. MOORE: Thank you. Dr. Neely?

DR. NEELY: This is Dr. Neely. I also voted yes, although it was definitely a little more reluctant than my prior vote for aspergillosis. I disagree. I think with the FDA's focus on placebo, I think the standard of care is amphotericin, and we need to be concerned about is this going to be worse than amphotericin. I don't think anybody would argue that it is better than placebo. So I think that was fairly well established.

But I think the larger question for me, or more important is, is it worse than amphotericin. And I think it really all comes down to slide 65 from the sponsor, which was the forest plot that had the overall effectiveness of isavuconazole in the 0103 cases, the Fungiscope and then compared to the historical controls.

And although the point estimate is no worse than any of the controls, the confidence interval of course is much wider because it's a much smaller population. So we are left with the possibility that isavuconazole may be worse than amphotericin in terms of efficacy, but we don't know. It's within that wider confidence interval.

So as Dr. Waterman said, I think the phase 4 surveillance study is going to be critical, and I really think the FDA ought to compel the sponsor to collect data to see where that mortality comes out for the patients who are treated with this.

I also think that this drug is going to be used, and I'm sure -- well, it's going to be used, even though this is not one of the labeling

requests by the sponsor today, but it is going to be used for empiric therapy in the setting of fever neutropenia and somebody who comes in with lung nodules, because essentially, to a clinician, it's going to be voriconazole plus Mucor, so all of a sudden it's going to be a very attractive therapy for the setting that I just mentioned.

So I think this is another study that the FDA ought ask the sponsor to do, is to formally evaluate isavuconazole in the empiric treatment of fever and neutropenia.

Let's see. In terms of labeling, I think it needs to be very clear in the label that this was never compared to amphotericin in a head-to-head, and that the label, if it so is labeled, is based solely on historical controls.

But I do think that we really have to take into consideration the absolute unmet need for therapy for this drug because there is the distinct possibility that it's at least as good as amphotericin, possibly even better. And it has certainly pharmacologic considerations that make it

very appealing compared to amphotericin, i.e., that is both IV and oral, and its safety profile is better.

Even though, again, it has not been compared head-to-head against amphotericin, we can certainly extrapolate I think its safety is improved compared to amphotericin by looking at the voriconazole comparative data, and we know that vori is safer than amphotericin.

So I think this drug really does fill an unmet need, and I have high hopes that it is at least as good amphotericin, but I do think we need more data to confirm that as time moves on.

So again, I think the label really needs to reflect that this was not done in a head-to-head comparison and is based on historical controls only. Because I think clinicians are going to have a little bit of trouble understanding when do they use amphotericin versus this drug. If they have somebody that they are strongly or even know has mucormycosis, what should be their first-line therapy? It is not clear at all.

DR. MOORE: Right. Thank you. Dr. Bennett?

DR. BENETT: I voted no because I was really unconvinced that this drug has clinically significant activity against mucormycosis. I'm also concerned that if the FDA sets the bar this low for a secondary approval, we'll be flooded with primary approvals for drugs that really should never reach the market.

Now, this drug will reach the market based upon aspergillosis, but you wouldn't want to reach the market based on mucormycosis. The standard of acceptance is so low that new drugs be accepted on the market with this kind of data, I think we have a terrible problem.

Now, in terms of the community experience, the elephant in the room that we've really not been talking about is posaconazole. And I think it should give some reassurance to the community that if a drug is approved for one indication, it will often be used for other indications, and that's what happened to posaconazole.

It's approved for preventing infections as

well as treating esophageal candidiasis, but it's very commonly being used for treating mucormycosis. And we're still finding out, years later, in what situations it might actually be useful, but it's certainly being used.

So the in the future Dr. Schueler's sons will certainly be able to get isavuconazole if there's a concern about mucormycosis because the FDA does not restrict the use once it's been approved for a primary indication. So I don't see any threat to the community by not approving it for mucormycosis, and I don't recommend the FDA do so. Thank you.

DR. MOORE: Thank you, Dr. Bennett. Dr. Chiller?

DR. CHILLER: Yes, thanks. I voted yes. And I think, again listening to Dr. Neely and Dr. Bennett, sort of hear the yes and no reasoning, I mean there are valid points there. I guess from my standpoint, I tried to look at the overall animal studies in this because there's so little human data, and that swayed my opinion and vote.

And also the fact that this is an incredibly rare disease, and we're just not going to get the robust studies that we all would like to see for this disease or, as we were talking before, for some other parasitic diseases that we work on, et cetera. There need to be approvals done with less than ideal amounts of data.

I guess my concern maybe for the label, or for discussion, as I've already brought up, is the idea that we are clumping mucormycosis into a disease entity and not into a staph aureus or a staph epidermis type of approval, so we're approving this drug to use for all species. All species are not the same, and there will be new ones.

So I'm not sure how that is addressed by the FDA, or how they deal with that, but that wouldn't cause me to pause and to vote no, or to say that it needs to be recommended for a specific type of species of fungi, but I just want to make that point. So as far as safety, I think we've all heard that where we feel on that, and I'll stop

there.

DR. MOORE: Thank you. Mr. Byrd.

MR. BYRD: Patient representative, Christopher Byrd. I voted yes, again, because I believe, from my perspective, there is an overriding need for treatment options for this patient population. Thank you.

DR. MOORE: Thank you. Dr. Andrews?

DR. ANDREWS: Yes. This is Ellen Andrews. I'm a consumer representative, and I voted yes. I understand the ambivalence about there being less information, but I understand an even more desperate patient, since there's only one other medication, and it's not perfect.

I think it's an improvement over current therapy, but again, we don't know. It shows some promise. And I take very strongly -- we will never have a perfect world to know for sure. As well as everyone around the table would like, we have to make our best guess, and that's what we've done.

One other thing that came to me after our last conversation is in discussing whether the FDA

approves something or not. If the FDA doesn't approve something, there is no label. There is no information that comes from the FDA. And the answer to a question about how will doctors know how to use this off-label, wink, wink, nod, nod, is it will all come from the drug company, and I'm not always comfortable with that. I don't know that I'm always going to be comfortable with that.

So in a question of when I do trust doctors and patients to look at the information and make the best choice among a lot of really lousy choices sometimes, and the more information they have from a balanced source, the better.

DR. MOORE: Thank you. Dr. Cappelletty?

DR. CAPPELLETTY: Diane Cappelletty. I voted yes. Again, I struggled a bit more with this one. The word "substantial" always sort of throws you initially, but being a rare disease, what is substantial for Mucor related is not the same as what it is for an aspergillosis. So that made me a little bit more comfortable with the numbers, although I think, with everybody else, I would like

to see more numbers if at all possible.

I was looking very closely as well at the slide that looked at outcomes, both the clinical outcome as well as the mortality outcome, based on whether it was used as primary versus refractory or intolerant. And when it was delayed in that therapy again, the disease has that much further to get ahead in those refractory patients. It makes it a little more challenging to treat them, and so yes, failure rates did go up the longer you delayed a therapy compared to when it was used as a primary, and when there were slight changes there.

To give clinicians an option for another choice, given the long durations of therapy, given the oral options, I think that will potentially be a game changer for treating this disease in the long run.

I agree with Dr. Neely that it's going to get used more broadly than, at least initially, for use, and that that's going to have to have some close monitoring. And I agree also with Dr. Chiller that more information regarding the

specific species of organism and outcomes related to it will be very important.

DR. MOORE: Thank you. This is Dr. Moore. I was very ambivalent about this one, and I really could have gone either way. I share Dr. Bennett's concern about -- certainly the drug, if it's approved for the indication of aspergillosis, will certainly be used for alternative indications, specifically mucormycosis. And it's true that using historical controls as merits for approval does set the bar fairly low.

On the other hand, as has been pointed out multiple times, this is an organism, an infection with a group of organisms which are difficult to see with significant frequency in order to conduct well-designed, open clinical trials. So we're kind of stuck with gathering data and inferring from other sources.

As I mentioned before the question, when stacked up against the amphotericin B data with the Kontoyiannis retrospective, I think it does merit a yes answer, from my standpoint, on this particular

point. Although again, I can't emphasize this enough with the FDA, that if this committee, as it appears to have done so, recommend approval of this drug, I wouldn't like to see this particular decision used as a precedent for the approval of other drugs with using strictly historical controls, and limited historical controls at that, for approval. Dr. Scheetz?

DR. SCHEETZ: Marc Sheetz. I used my vote as a non-vote to abstain, largely for the reasons we've heard from the committee. I think everybody that's voted one way has made some comments to the other side. The question is, should clinicians have this in their armamentarium? I think the answer wholeheartedly is yes.

When we heard from the community, we heard from patients that are afflicted with this disease, and we try here to look at numbers, but always think about the fact that the numbers represent people. So I think there should certainly be options.

Now should it be labeled? I'm not really

sure how to answer that question. As Dr. Neely pointed out, if we were to run the statistics, this probably would not meet non-inferior margin.

I'm also not sure that they've really shown a concordance from the animal data that's been either allometrically scaled or linked to human data. So I think there could certainly be some more work linking what they've seen in animals to what actually occurs in humans.

I think there's a relative lack of pharmacokinetic, pharmacodynamics, pharmacotoxic data that we've actually seen today, and I think that makes it hard for me, again, to say yes. But again, should clinicians have options?

I believe that that should be true, especially with a disease that's this dire and this rare. But if it's approved for another indication, should it also have this indication on labeling? I'm not sure I can answer yes to that.

DR. MOORE: Thank you. Dr. Shyr?

DR. SHYR: Yu Shyr. I vote yes. Now, really, I wish I have a continuous outcome in front

of me instead of dichotomous yes or no. So I vote yes really barely over 50, maybe 50.1 percent. Let me tell you the reason.

If it looked non-randomized single-arm historical control study, what is the most important things we look with this data? It's how you select your control match, right, so that is the most important thing. That's really -- I think unfortunately I don't have the data. We have more than 900 amphotericin B data as a control data. We couldn't find a good way to really use a propensity score or any other better statistical method to match or find a better control to get a good answer.

There are two reasons really I vote yes, then I will come back to the other comments. The first reason is we looked at safety profile. All the safety profile looked -- more than 90 percent of safety profile, the applicants did show that this drug is safe. Okay. It's safe though we didn't reach a statistically significant level, but all the data, each category, we do show, so that's

how I feel. The safety profile is very nice.

Second is the question FDA put onboard. The question is, is the efficacy -- we're not really talking about the non-inferior now. So if you really compare to the placebo, yes, I do believe, even with this limited 21 patients, it did show it's better than the placebo group. So that's why, because the question now asks, we are in charge, we have to answer, is yes or no, so that's what I vote.

But I do think we need to pay attention to following. There is no evidence that this drug can show either non-inferior or as good as amphotericin B. That is the truth. The data cannot show that, and that's number one.

Then number two, I totally echo the previous comments, we need to have a phase 4 postmarket, have to be very careful to monitoring all the true -- the efficacy, the rate for this. But again, I understand, this a rare orphan disease. We don't have enough cases to conduct real good randomized trials. But anyway, that's all my

comment.

DR. MOORE: Thank you. Dr. Follmann?

DR. FOLLMANN: Thanks. This is Dean Follmann. I voted no. This is a hard decision for me to make also, as I think it is for many panel members. There are a few points I wanted to bring out I guess.

First of all, the FDA did a comparison of the death rate for their 37 or 21 with probable or known disease and compared that to a group that had a 6-day delay. I thought that was a relatively straightforward analysis, or simple analysis, and better analysis could have been done. We don't know if the two groups were balanced or not. I suspect that they weren't balanced. And so there could have been more statistically sophisticated methods to see if there really was an advantage over placebo.

I believe there would be, but as I mentioned in my comments earlier, I don't think that's, from my perspective, really the relevant question. I think for me the more relevant question is how does

it compare to amphotericin B? And for that, we look at what the sponsor did with the case control study, which was quite underpowered, understandably because it's relatively rare. There are few people with definite or probable disease.

Another point I want -- and so I didn't find that very compelling. But another important point I wanted to make out, in that study that the sponsor did, there were about 75 percent of the patients who didn't have disease. We don't know what their death rate is, much less what it would compare to amphotericin B.

So I think that analysis has to be done to reassure ourselves that in that group that don't have mucormycosis, is the death rate similar in patients who would get amphotericin B. And if it's a much higher death rate, there's no way we should approve this.

I have no real reason to suspect it one way or the other, but I think just due diligence, we need to see the evidence and the data to assure ourselves that that's in fact the case.

DR. MOORE: Thank you. All right, so to briefly summarize, I think it's probably best to say that the panel was hesitant to move forward with the recommendation for approval, the main reason being that the data presented were based upon historical controls, which were not -- so there was no direct comparison with amphotericin B in any form with the study drug.

As such, this becomes problematic in recommending approval. Nevertheless, given the significant limitations in gathering data, the drug does seem -- at least based on the data presented, it appears to be effective.

Unless somebody has an additional -- yes, Dr. Robinson?

DR. ROBINSON: Yes, it's kind of a coda to all of this discussion. I think, regardless of what one's opinions are of the data and how they turned out today, I think the agency deserves a congratulations and a thank you for bringing forward, in an innovative way, this assessment of a drug for rare but very critical high need

indication.

DR. MOORE: I would agree with that. I also want to personally thank the presenters in the open public hearing for their very moving and terrific presentations. Thank you very much. I know it took a lot of courage to come and tell your son's story, Mr. Schueler, but I want to tell you that -- I think I can safely speak on behalf of the entire committee that that was a very moving tribute, and I'm sure your son would be very proud. Thank you.

Before we adjourn, are there any last comments from the FDA. Dr. Nambiar?

DR. NAMBIAR: Sure. Thank you, Dr. Moore. We'd like to thank the committee members for their participation in today's advisory committee and for providing us with very useful advice. As always, in addition to your yes/no votes, we greatly benefit from all the discussions. We just need to take all this back and synthesize it and move forward.

We would also like to thank the applicant

for all their work on this NDA and their presentations today. And as you've said, our many thanks to the speakers at the open public hearing. Wish you all safe travels. Thank you.

DR. MOORE: Wait, before we adjourn, Dr. Bennett has one more comment to make. Dr. Bennett? The disembodied voice of Dr. Bennett. So we have him on the line?

DR. BENNETT: It is. I would like to point out that those of us who are sure that amphotericin B has a role in treating mucormycosis are basing it much less on the immunocompromised patient than in a diabetic ketoacidosis. And the published theory of that disease indicates that mortality rate is actually 50 percent. Now, that's very high, but it's based upon controlling the diabetic ketoacidosis, doing appropriate surgery, but also use of amphotericin B. And I think there's really no doubt that the drug works in that situation.

The problem with treating an immunocompromised host is that individual patient,

it's very hard to say if it's works. So I think trials in this particular background are never really going to be convincing. So I wonder what the FDA could do to kind of nudge it along, and that as you can't approve a drug for a primary indication, maybe they could approve for it for salvage indication, just indicating, gee I'm not so sure it should be used as primary therapy from the kind of data that we have in this particular population. So that's all I had to say, Tom.

Adjournment

DR. MOORE: Thank you, Dr. Bennett.

If there are no further comments, we will now adjourn the meeting. Panel members, please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thanks everybody.

(Whereupon, at 2:18 p.m., the meeting was adjourned.)